GROWTH
Genetics & Hormones
Vol. 3 No. 1 March 1987

Lawson Wilkins—Pioneer in Pediatric Endocrinology and Growth Disorders

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Chairman, Editorial Board
Growth, Genetics, and Hormones

Twenty-four years have passed since 1963, when Dr. Lawson Wilkins died at the age of 69. His demeanor, his accomplishments, and the esteem in which he was held by his peers and his extended family of pediatric endocrine fellows whom he trained are not known to the third and fourth generations of pediatric endocrinologists who are members of the Lawson Wilkins Pediatric Endocrine Society. Since volumes could be written about each aspect of Dr. Wilkins's life, an abbreviated biography is inadequate. Nevertheless, a brief history of Dr. Wilkins's life presents the opportunity to enhance the image of a man who should not be forgotten by pediatric endocrinologists. pediatricians, or geneticists.

Lawson Wilkins was born in 1894 in Baltimore. His father, Dr. George Wilkins, was probably the most highly respected family practitioner in the city. Historical accounts indicate that George Wilkins was intellectually curious, dedicated to his patients, and attentive to detail. His son exhibited the same characteristics. Mrs. Wilkins's death, when Lawson was five years of age, significantly strengthened the already close bond between father and son.

After receiving a baccalaureate degree from Johns Hopkins University in 1914, Lawson Wilkins began medical school there; in 1917, along with many other medical students, he volunteered to go to Europe and serve as an orderly in a medical unit during World War I. After the war, he was accepted as an intern in internal medicine at Yale for a year. He then returned to Baltimore to serve a pediatric internship at Johns Hopkins, where the influence of Drs. Blackfan, Park, Kramer, and the other giants of pediatric medicine of the period further whetted his keen intellectual appetite.

But it was most likely his desire to follow in his father's footsteps that prompted him to enter pediatric practice in Baltimore in the early 1920s. Until the time he accepted a full-time academic position in 1946, Dr. Wilkins had practiced pediatrics for 25 years with intense intellectual curiosity and great compassion for his patients. This author has on several occasions met adults in Baltimore who remembered Dr. Wilkins fondly as their pediatrician. These individuals had no idea that Dr. Wilkins had made major contributions to medicine as an endocrinologist and a geneticist.

In 1935, Dr. Edward Parks, who was instrumental in the development of various subspecialties in pediatrics, invited Lawson Wilkins to establish an endocrine clinic in the Harriet Lane Home of the Johns Hopkins Hospital. Dr. Wilkins was reluctant, since endocrinology at that time was the trade of quacks and charlatans. He accepted the position, however, and with Drs. Fuller Albright, John Eager Howard, George Thorn, Robert Williams, and a few others, he transformed endocrinology into a respectable subspecialty.

Wilkins focused on the problems in pediatric endocrinology—particularly problems of growth and genetics—while his confreres tended to the accumulation of knowledge about endocrinology in adults. Although he was intensely interested in the metabolism and control of carbohydrate and fat metabolism, he assiduously avoided a clinical interest in diabetes. Possibly this was because Dr. Harriet Guild of the Harriet Lane staff had established a diabetes clinic and, characteristically, Dr. Wilkins would not intrude on the

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work of others unless invited. Interestingly, he never considered diabetes a disease of the endocrine system, although he believed hypoglycemia was.

Scientific Contributions

Lawson Wilkins greatly expanded our knowledge of endocrine physiology and pathophysiology. Some of us have been fortunate enough to have shared in his experiences in establishing pediatric endocrinology as a subspecialty. Drs. Bongiovanni, Migeon, and Eberlein shared his interest in adrenal steroid metabolism and the pathophysiology produced by deficiencies of various enzymes for cortisol synthesis, including defects in 21 hydroxylation and 11 hydroxylation that produce congenital virilizing adrenal hyperplasia. In 1950, Drs. Crigler, Klein, Gardner, Migeon, and Rosemberg joined Dr. Wilkins in successfully treating the first patients with congenital virilizing adrenal hyperplasia with cortisone. As always, Dr. Wilkins applied the knowledge he gained from his physiologic studies to therapy.

Drs. Grumbach and Van Wyk worked with Dr. Wilkins in his studies of sexual differentiation. In this area, Dr. Wilkins applied what had been learned from the animal experiments of Alfred Jost to postulate and prove that the anatomy in gonadal agenesis and pseudohermaphroditism in human beings could be explained by the presence or absence of androgens and Mullerian inhibiting factor.

It was with Dr. Wilkins that Gardner developed his interest in genetics and cytogenetics. It was Dr. Wilkins and his students who were among the first to apply the cytological techniques of Dr. Murray Barr to identify the inactivated X chromosomes (Barr bodies) in the nuclei of patients with Klinefelter's syndrome and in female pseudohermaphrodites. These diagnostic aids facilitated the diagnosis and therapy of patients with abnormalities of sexual development.

With Dr. Wilkins, Clayton demonstrated that enzyme defects in the synthesis of thyroid hormone metabolism produce pathologic changes in the thyroid that simulate thyroid carcinoma. Dr. Wilkins had previously demonstrated during his years in practice the effect of thyroid hormone on cholesterol and creatinine metabolism.

These were classic physiologic studies, in which the effects of a hormone were investigated clinically. He had demonstrated during this same period that the epiphyses in patients with thyroid deficiency were misshapen as they calcified (epiphyseal dysgenesis) and delayed in appearance, and that epiphyseal dysgenesis was a frequent finding in the untreated cretin. With treatment, the epiphyses that had not appeared because of thyroid hormone deficiency were often dysgenetic when they did appear, but the epiphyses that were expected to appear after treatment was begun were always intact in their development.

David Smith and this author benefitted from Dr. Wilkins's astute recordkeeping; he was a master in maintaining growth charts and other documents. With him, we published the effect of thyroxin treatment on the mental development of cretins.

The Second Generation and Beyond

Other pediatric endocrinologists from the United States who trained with Dr. Wilkins between 1946 and 1960 were Drs. Shepard, Holman, Cara, Mosier, Cleveland, David, Green, Martin, Silverman, and Stempfel. Many students from abroad who are now professors also trained with Dr. Wilkins. These include Drs. Bertrand, Eckert, Gerrard, Bergada, Papadatos, and Prader. These endocrinologists and professors have trained the third generation of pediatric endocrinologists, who in turn have trained the fourth generation.

Dr. Wilkins wanted to be called "Lawson" by "his boys" as he

Lawson Wilkins plotting metabolic data from a patient with endocrine disease. It was Dr. Wilkins's compulsive accumulation, plotting, and analyses of such data that transformed the subspecialty of pediatric endocrinology into a highly respected scientific discipline.

GROWTH DISORDERS—PARENT SUPPORT GROUPS

CANADA

Achondroplasia (Short Stature)
Little People of British Columbia
P.O. Box 453
Abbotsford, BC V2S 5Z5

Osteogenesis Imperfecta (Brittle Bones)
Osteogenesis Imperfecta Society
Box 607, Station U
Toronto, Ontario M8Z 5Y9

Prader-Willi Syndrome
Prader-Willi Association of British Columbia
69 East 46th Avenue
Vancouver, BC V5W 1Z2

Turner Syndrome
Turner Syndrome Support Program
c/o Susan Charney
York University
Counselling and Development Centre
4700 Keele Street
Toronto, Ontario M3J 1P3

UNITED STATES

Achondroplasia
Human Growth Foundation
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Baltimore, MD 21201

Northwest Chapter
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P.O. Box 15364
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Little People of America, Inc.
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Anorexia/Bulimia
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Arthrogryposis
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CARING—a nonprofit organization
P.O. Box 400
Milton, WA 98345

Down's Syndrome Letters
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Oxon Hill, MD 20022

Parents of Children with Down's Syndrome
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Houston, TX 77035

National Association for Down's Syndrome
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282 W. Fullerton
Addison, IL 60101

Parents of Down's Syndrome Children
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Silver Spring, MD 20902
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Down's Syndrome Association
First United Methodist Church
1709 Frederick Street
Cumberland, MD 21502

Dysautonomia (Riley-Day)
Dysautonomia Foundation, Inc.
Ms. Lenore F. Roseman, Executive Director
370 Lexington Avenue, #1508
New York, NY 10017
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Ectodermal Dysplasia
National Foundation for Ectodermal Dysplasias
108 North First, Suite 311
Mascoutan, IL 62258
(618) 566-2020

Fetal Alcohol Syndrome
National Clearinghouse for Alcohol Information
P.O. Box 2345
Rockville, MD 20852

Fetal Alcohol Syndrome
c/o Mr. David Johnson
Bureau of Alcohol and Other Drug Abuse
Department of Health and Social Services
1 W. Wilson Street
Madison, WI 53702
(608) 266-7585

Lowe's Syndrome
Lowe's Syndrome Family Newsletter
c/o Kaye McSpadden
607 Robinson Street
West Lafayette, IN 47906

Maple Syrup Urine Disease
Families with Maple Syrup Urine Disease
Rte. #2, Box 24A
Flemingburg, KY 41041
(606) 849-4679

Mucopolysaccharidosis
The Mucopolysaccharidosis (MPS) Society, Inc.
c/o Mary Majure
556 Central Avenue
Bethpage, NY 11714

Neurofibromatosis
Joan C. Rudd, President
National Neurofibromatosis Foundation
70 West 40th Street
New York, NY 10018
(212) 689-9034

Physicians may feel free to make photocopies of this Support Group List and distribute them to their patients.

Neurometabolic Disorders
Association of Neurometabolic Disorders
2707 Cheltenham Road
Toledo, OH 43606

Organic Acidemia
Organic Acidemia Association
c/o Lorie Aster
1532 South 897th Street
Kansas City, KS 66111

Osteogenesis Imperfecta
The American Brittle Bone Society
712 Dartmouth Avenue
Cinnaminson, NJ 08077

Osteogenesis Imperfecta Foundation, Inc.
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Hot Springs, AR 71901
(501) 525-1272

Osteogenesis Imperfecta National Capital Area, Inc.
Mrs. Margaret Cauffield
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Phenylketonuria
PKU Parents Group
Mrs. Donna Jahn, President
518 Paco Drive
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Prader-Willi Syndrome
Prader-Willi Syndrome Association
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Edina, MN 55436
(612) 933-0133

Spina Bifida
Spina Bifida Association of America
Mr. Kent Smith, Director
343 S. Dearborn Street, Suite 319
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Spina Bifida Association
Pat Roberts, President
10524 197th Street N.W.
Bothell, WA 98011

Tuberous Sclerosis
National Tuberous Sclerosis Association
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National Tuberous Sclerosis Association
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Tuberous Sclerosis Association of America
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Turner's Syndrome Support Group
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NATIONAL CLEARINGHOUSE FOR GENETIC DISEASES

Association for Glycogen Storage Disease
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Cartilage Hair Hypoplasia
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Association for Research into Restricted Growth
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Down's Syndrome Congress
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Dystonia Foundation
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Melville, NY 17747
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Dystonia Medical Research Foundation
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Dystrophic Epidermolysis Bullosa Research Association of America
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Downstate Medical Center
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Epidermolysis Bullosa Research Association
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Brooklyn, NY 11229

Gaucher's Disease Registry
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Human Growth Foundation
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Little People's Association of Australia
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called those who trained under him, but esteem for him was so great that he remained "Dr. Wilkins" to most for many years.

It is not by chance, however, that there was only one female fellow, Dr. Eugenia Rosemberg, prior to 1960. It was simply Dr. Wilkins's policy not to accept women as fellows. He respected the intellect of female physicians, but he was reluctant to let them examine the male teenagers who came to him for consultation. With the acceptance of Drs. JoAnne Brasel, Virginia Weldon, and Irene Solomon as pediatric endocrine fellows at Johns Hopkins in the early 1960s (when he was professor emeritus but still active), he relented and realized that he had been unduly restrictive.

Lawson Wilkins was more than a scientific giant. He was a man of great magnetism and personality. Few who knew him could forget his bass voice, which he put to good use singing ballads and bawdy songs long into the night. He loved to sail his boat on the Chesapeake Bay and tell jokes, which he masterfully embellished. He also adored—and was adored by—Lucile Mahool, his first wife, and Teence Anderson, to whom he was married after Lucile died in 1959.

At a meeting in Baltimore of the Lawson Wilkins Pediatric Endocrine Society in the mid-1960s, Dr. John Eager Howard related the following about Dr. Wilkins: "When I first met Wilkins, which was at a time I had heard about his studies that Dr. Park exalted, I was even more impressed by the vitality of the man than by his scientific studies. In response to my knock on the door, the rafters fairly reverberated to the booming voice that urged us to come in. His whispers in a conference could cause consternation, for his 'That fellow is putting out pure hogwash' might have been heard all over the room. But I should hasten to say that his comments were rarely uncomplimentary, for an immense generosity toward others was one of his most endearing qualities." In accord with Dr. Howard's observations, this author found Dr. Wilkins to be a paradox in that he was gruff but gentle. And while he always dominated the situation, he never exhibited dominating behavior toward individuals.

Another mark of the quality of Dr. Wilkins's personality was the grace with which he relinquished his pediatric endocrine clinic and training program to Dr. Claude Migeon and this author in 1960. During the next three years, before he died in 1963, he was present much of the time, he remained intellectually curious, and he continued to contribute in all respects.

We in pediatric endocrinology and genetics are indeed blessed to have had such a man to lead us. The history of Lawson Wilkins is well worth passing along to the third and fourth generations of pediatric endocrinologists, and it is to be hoped that they will pass it along to the fellows who train with them.

Special Report: International Symposium: Growth Hormone and Growth—October 8-10, 1986, Buenos Aires, Argentina

Robert M. Blizzard, M.D.
Chairman, Editorial Board
Growth, Genetics, and Hormones

The conference began with three presentations on normal growth. Dr. Prader (Switzerland) emphasized that growth, skeletal maturation, the timing of puberty, and adult height are genetically programmed. Thus, we can predict adult height and compare it with target height, which is estimated from midparental height. The tempo of maturation and the final height are independent multifactorial variables that allow us to understand the classic variations. According to Dr. Prader, maturational variations may possibly be mediated by physiologic variations in the hypothalamic control of growth hormone (GH) secretion.

Dr. Prader also noted that although the sex hormones have little influence on adult height, they do accelerate growth and decrease adult height when they are present too early and in large amounts.

Dr. Tanner (England) discussed the prediction of adult height in normal and pathologic conditions. He emphasized that the predicted height of patients is probably the best single index of the success or failure of treatment. Dr. Tanner pointed out that the Bailey-Pinneau (BP) method of predicting height, using the Gruelich-Pyle atlas, is not as accurate as other methods and should not be used. The Tanner-Whitehouse (TW-2) method is the method of choice.

Dr. Lejarraga (Argentina) reported on a comprehensive multicenter study to determine normal growth curves for children in Argentina. His data indicate that during the past 50 years, the ultimate height has increased by 10 cm in boys and 8 cm in girls.

The second major topic discussed was the normal hormonal relationships of the "hypothalamic-pituitary-peripheral" axis for GH secretion and action. Dr. Illig (Switzerland) explained that testosterone priming, which enhances the release of GH, can be

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used to diagnose boys with constitutional delay of adolescence (CDA). GH peaks are measured following the administration of the stimulating agents, arginine and insulin. These data suggest that GH production may be increased with adolescence. Dr. Bierich's data regarding the integrated concentrations of growth hormone (ICGH) in normal boys at various stages of adolescence also indicated that GH production goes up at adolescence under the stimulus of sex steriods. These data also showed that ICGH in patients with CDA are lower than those in children of the same chronological age who are not delayed.

Dr. Van Wyk (USA) emphasized that somatomedin-C (Sm-C) or insulin-like growth factor I (IGF-I) is a modulator whose major role is to amplify other hormonal signals for a wide variety of growth processes. These include ovarian function, in which IGF-I potentiates the actions of follicle-stimulating hormone (FSH) in rat granulosa cells, and the synthesis of estrogens and luteinizing hormone (LH) receptors. Dr. Van Wyk also discussed the need for IGF-I and epidermal growth factor to work together to produce mitogenesis in mouse fibroblasts. He emphasized that somatomedins have autocrine and paracrine as well as endocrine functions. Nanomolar and, in some cases, picomolar concentrations of IGF-I stimulate a wide variety of physiologic processes, which—together with other growth factors—control growth in a quite different manner than has been thought in the past.

Dr. Blizzard (USA) presented data from the University of Virginia, which showed that growth-releasing factor (GRF) can stimulate GH release, even when given over 14 days with no down-regulation of GRF on GH release from the pituitary.

The third major topic concerned the diagnostic tests used in children with short stature. Dr. Blizzard has found that the two-site immunoradiometric assay (IRMA) has distinct advantages in measuring GH in serum. Although measuring ICGH can assist in diagnosing GHD, some authors believe that a rise in ICGH is often superfluous.

ICGH tests done at night, preferably over 12 hours, are often adequate when comparing patients with short stature. The IM9 receptor cell assay is the only practical receptor assay at this time.

Dr. Van Wyk stated that the bioassays for IGF-I are expensive, tedious, not specific, and may provide misleading results because of inhibitors. In contrast, the radioimmunoassay for IGF-I has the potential for high specificity. However, it does not accurately measure IGF-I when unextracted plasma is used because of the presence of binding proteins. Nonetheless, Dr. Van Wyk believes that this assay has diagnostic value if we remember that values depend on factors other than GH, eg, starvation, thyroid, prolactin, and estrogen levels.

Dr. Jasper (Argentina) presented data showing that patients receiving GH often grow, even in the absence of increased IGF-I levels. Many discussants at the conference agreed with these findings, but all remained perplexed by these observations.

Other speakers discussed abnormal GH production and action in children. Dr. Illig reviewed the various types of genetic GHD and the gene cluster that is responsible for the synthesis of GH and human placenta lactogen or human chorionic somatomammotropin. She pointed out that to date the only gene defect shown to account for GHD is found in type 1A GHD patients. Surprisingly, not all of these patients have had cessation of growth with GH treatment, even though antibodies to GH have developed consistently.

Dr. Laron (Israel) discussed the syndrome named after him. He emphasized that GHD may possibly lead to "less than expected" mental development. A lively discussion ensued on whether GH could have such an effect in utero or immediately after birth.

Dr. Eshkol (Switzerland) of Serono Laboratories in Geneva reviewed the preparation of GH by means of mammalian mouse tumor cells (currently being tested at Serono Laboratories). She also discussed additional purification procedures for native pituitary GH, which is still available in South America, Europe, and elsewhere.

The use of GH and other growth-promoting agents in both GHD and non-GHD patients was also a major topic. Dr. Jasper reported on the use of very small doses of ethinyl estradiol to increase growth rates in patients with Turner's syndrome. This result is comparable with the findings reported by Dr. Levine-Ross at the September 1986 NICHD workshop, Advances in Research in Human Growth.

On the other hand, several speakers commented that estrogen may not be preferable to other agents in treating patients with

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Growth, Genetics, and Hormones is published by Biomedical Information Corporation under an educational grant from Genentech, Inc. The information in this publication reflects the views of the editors and does not necessarily reflect the opinions of the sponsor or the publisher.

Turner's syndrome. Dr. Stahnke (West Germany) reported the use of oxandrolone (Anavar) in 37 patients treated over 10 years. In these patients, height increased over the first year and, in some, persisted during the second year. The height age to bone age ratio was not adversely affected.

The use of GH in Turner's syndrome was discussed by Dr. Raiti, who directed a collaborative project through the NIH's National Hormone Distribution Program. Although, in general, growth rates increased, the effect of GH on ultimate heights could not be determined, since the program was disrupted when GH was withdrawn from distribution because of the Creutzfeldt-Jakob disease incident. In his study, Dr. Raiti noted that GH did not always increase growth rates while Dr. Stahnke reported that six of eight of his Turner's syndrome patients treated with GH had increased growth rates.

Dr. Bierich presented results from a collaborative study in Germany using Somatonorm® KabiVitrum in GHD patients. The study patients had a very positive growth response and when recent preparations were used, they exhibited only a minimal antibody response. The growth responses were inversely related to the initial height and the degree of bone age delay, and were directly related to the genetic tendency for tall stature and to a diagnosis of isolated GHD (when compared with multiple hormone deficiencies).

Dr. Bierich also has demonstrated that GH treatment increases growth velocities in patients with constitutional delay. However, he feels that treatment should be reserved for the few patients in whom this agent may be preferable.

Drs. Tanner and Bierich discussed the desirability of increasing the dosage of GH when puberty begins, since GH production very possibly may be increased during normal puberty. Dr. Laron commented that GH may have an additional action on growth of the penis, which is another possible reason for increasing the dosage of GH in males at puberty.

Drs. Poskus and Retegui (Argentina) presented papers on antibodies to GH and the use of monoclonal antibodies to identify the sites on the GH molecule that allow for binding to receptors. These types of studies someday could allow us to identify patients with immunologically active, but biologically inactive, hormone.

Dr. Raiti discussed some of the problems that may arise during treatment with GH. He emphasized that to his knowledge no patients have developed diabetes while receiving GH. Reports indicate that there may be an increased incidence of slipped capital femoral epiphyses in patients treated with GH. With the possible exception of one case in New Zealand, there have been no additional cases of Creutzfeldt-Jakob disease in patients who have received GH.

Dr. Laron emphasized the need for team counseling of GHD patients. If GHD has been diagnosed and treated in early infancy or childhood so that the child grows at a relatively normal rate, many psychological difficulties can be avoided.

Special Report: Laurentian Hormone Conference—August 24-29, 1986, Montebello, Quebec

Alan D. Rogol, M.D., Ph.D.
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Growth, Genetics, and Hormones

At this conference on hormones, Dr. Anthony Cerami reviewed the status of cachectin—a macrophage protein that induces the catabolic state. This new hormone-like activity is increased in the circulation under conditions in which the predominant mode of metabolism is catabolic. Whether different types of stress—eg, starvation, cancer, or burns—induce a similar hormone is not yet determined. Because the activity measured is very similar to that of the tumor necrosis factor, cachectin may be a member of a family of hormones with activities opposite to those of the somatomedins.

Dr. Robert Ryan reviewed the structural requirements for the binding of the gonadotropins to their receptors. Not only are there peptide-binding domains, but there are also specific sites of the receptor complex that bind the complex carbohydrate chain. These are separate membrane constituents called lectins. This complex interaction leads to the microaggregation of the receptor complexes and is absolutely required for activation of the adenyl cyclase second messenger system.

Specific domains within the primary sequence of the alpha (and beta) subunits have been described; these subunits are crucial to the tightly constrained, folded structure of the alpha-beta dimer. Significant structural changes do not allow subunit binding and thus produce biologically inactive molecules.

Dr. Patricia Donahoe reviewed new data on the molecular biology of mullerian-inhibiting substance (MIS)—the fetal regressor for the mullerian system in the male fetus. This substance is very closely related to tumor necrosis factor and

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may have important therapeutic value in cancers of the reproductive tract in females as well as in males. The biology of the material is influenced by the ambient steroid hormone levels, with androgens increasing and estrogens decreasing the MIS activity. This is probably why there is no expression of MIS activity in the female fetus. In the ovary, its probable mechanism of action is that of meiosis inhibition.

In a cultured cell line, MIS is able to inhibit the phosphorylation of the epidermal growth factor (EGF) receptor by inhibiting the tyrosine kinase activity of the liganded receptor. This may be the fundamental mechanism of action—inhibiting the transmembrane signalling of liganded growth factor (and growth-inhibiting) receptors.

Dr. Robert Lefkowitz discussed his continuing work on the mechanism of homologous desensitization of the beta-adrenergic receptor. He described a new enzyme, beta-adrenergic–receptor kinase (BARK). As desensitization to agonists occurs, this enzyme moves from the cytosol to the membrane. There are striking similarities to the rhodopsin kinase of the visual system that is "homologously desensitized" by light. BARK is able to phosphorylate only the desensitized receptor. An agonist-induced change in membrane protein allows phosphorylation in the carboxyterminal serine and threonine-rich region. This leads to the uncoupling of the receptor from the cyclase enzyme, sequestration of the receptor, breakdown by phosphatase activity, and regeneration of functional activity as the receptor returns to the membrane. The enzyme can affect a number of receptors so that the *specificity* of this process is built into the specificity of the liganded receptor.

Special Report: The David Smith Workshop on Malformations and Morphogenesis—August 1986, Burlington, Vermont

Judith G. Hall, M.D.
Associate Editor
Growth, Genetics, and Hormones

A variety of new clinical syndromes were described at this meeting and a number of well-known conditions were revisited. The hypertelorism hypospadias (BBB) syndrome and the hypertelorism dysphagia (G) syndrome were discussed in some detail; the suggestion that they may actually be alleles or the same condition was supported by much of the discussion.

A number of the papers presented suggested that pigmentary abnormalities in the presence of mental retardation with or without additional congenital anomalies may be an indicator of chromosome mosaicism. This finding has been well demonstrated in tetrasomy 12p mosaicism (Pallister-Killian syndrome); pigmentary streaking is also seen in diploid/triploid/mixoploidy. A number of unusual patients were presented in detail at the meeting. Many of these patients had normal leukocyte chromosome studies, but chromosomal mosaicism was apparent in fibroblast chromosome studies. Hypomelanosis of Ito (streaky areas of decreased pigmentation with asymmetry in the size of the two sides of the body) is a syndrome deserving further study; it was suggested that it may represent chromosomal mosaicism. The take-home message was that fibroblast cultures should be strongly considered for patients who have normal peripheral blood chromosomes, pigmentary abnormalities, mental retardation, and short stature with or without additional anomalies.

Several new observations were made concerning neural tube defects. Careful autopsies of children who had spina bifida with no additional congenital anomalies showed marked abnormalities of blood vessels to the affected part of the spinal cord and vertebral area. It is not clear whether this change is a primary or secondary disturbance. A distinction can be made between high neural tube defects (primary neurulation defects) and lower neural tube defects (canalization defects) in terms of the recurrence risk for having another child with a neural tube defect. Lower neural tube defects appear to have much less risk of recurrence for the family. Brain stem auditory evoked potentials may be a useful way of determining whether or not a particular patient with meningomyelocele has abnormal brain development.

The recent film and play about John Merrick, the " Elephant Man," focused a great deal of attention on neurofibromatosis, which was addressed in an interesting presentation. The "Elephant Man" may not actually have had neurofibromatosis. Review of the autopsy findings on John Merrick and the historical information that is available today strongly suggest that it is much more likely that he actually had the Proteus syndrome, a condition described by Wiedemann and characterized by ham-

artomatous overgrowth.

Several presenters reviewed the accuracy of prenatal ultrasonic diagnosis for congenital anomalies and suggested that the technique may be only 50% accurate unless one focuses on a particular body area or knows what to suspect in a particular area. Thus, the physician should alert the ultrasonographer if there is an area of concern when careful examination is indicated. It was strongly recommended that fetal karyotyping of amniocytes be done when a structural abnormality is found on ultrasound during the third trimester. Indeed, a chromosomal abnormality is present in as many as one third of cases in which congenital anomalies are detected during the third trimester. Knowing that a chromosomal abnormality is present may alter management.

A new syndrome that may be quite common was described. The urofacial syndrome consists of obstructive urologic problems seen in association with abnormal facial muscular movement, so the child's smile looks more like a grimace. Intelligence is normal, and the condition probably has an autosomal recessive inheritance.

It would appear that Pena Shokeir syndrome (an autosomal recessive syndrome characterized by congenital contractures and hypoplastic lungs) is not a diagnosis but rather a phenotype that results from decreased intrauterine movement of the fetus and is attributable to many different causes. Thus, when any of the features of the Pena Shokeir phenotype (intrauterine growth retardation, congenital contractures of limbs, craniofacial anomalies, hypoplastic lungs, short umbilical cord, or polyhydramnios with short gut syndrome) is present, physicians should look for the other signs in the newborn infant. A variety of pathologic findings have been seen in babies diagnosed as having Pena Shokeir syndrome. However, the reported familial cases are all probably autosomal recessive disorders, and prenatal diagnosis should be offered for any future pregnancies.

Special Report: 25th Annual Meeting of the European Society for Pediatric Endocrinology—August 31-September 3, 1986, Zurich, Switzerland

Jürgen R. Bierich, M.D.
Associate Editor
Growth, Genetics, and Hormones

In a round table discussion that opened the meeting, Drs. Raiti and Kaplan reported on the use of biosynthetic human growth hormone (hGH) preparations in the United States, while Drs. Job (France) and Preece (England) reported on their use in Europe in patients with classic pituitary dwarfism. In all studies, the results were comparable with those obtained with native pituitary hGH. Initially, patients developed high titers of antibodies to growth hormone. Subsequent improvements in purification techniques significantly reduced antibody incidence to that seen with the highly purified native pituitary preparations. Low titers are clinically meaningless and do not inhibit growth.

Drs. Albertson-Wiklund (Sweden), Bierich (Germany), and Brook (England) discussed the use of hGH in nonclassic hypopituitary short stature. The results were excellent in patients with constitutional delay of growth and adolescence and in those with partial growth hormone deficiency (GHD). Spontaneous growth hormone (GH) secretion was diminished in both types of patients. Thus, hormone treatment serves as replacement therapy. Girls with Turner's syndrome also were successfully treated in many cases.

Dr. Prader (Switzerland) reported the results of two large longitudinal growth studies in Zurich. According to the data, the secular acceleration of growth and maturation has been constantly positive for decades in young men, but this appears to be no longer true for infants. Prior to puberty, body height and growth velocity are identical for both sexes. Differences appear with the onset of the pubertal growth spurt, which starts at age 10 in girls and at age 12 in boys. This growth spurt is much more rapid in boys than in girls, and explains the difference in height between adult men and women. Sex hormones are responsible for the pubertal growth spurt but not the final height. In contrast, the midgrowth spurt, which occurs at age 7, is independent of sex and gonads and corresponds to the adrenarche.

Stanhope et al (England) reported on the mechanism of the pubertal growth spurt induced by pulsatile gonadotropin-releasing hormone (GnRH) treatment. Twenty-six normal short patients received GnRH subcutaneously for 90 minutes each night for ten to 16 months. The girls immediately began to secrete increased amounts of GH. The pulse amplitude was increased but not the number of pulses. In contrast, boys first demonstrated a growth deceleration and diminution of GH secretion. During maturation and coinciding with a testicular volume of 10 ml, GH secretion increased and the pubertal growth spurt occurred. Hindmarsh et al, who are in the same investigative group, found a highly significant positive correlation between growth velocity and circadian GH secretion. This led these researchers to administer hGH subcutaneously, 2 IUs each night for six-month peri-

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Special Report: ESPE Meeting

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ods, to 17 children with short stature. A gain in growth velocity (SDS) from −0.49 to +2.86 was observed.

Most idiopathic GHD is attributed to perinatal lesions. However, the pathogenesis of these processes is still unclear. Charlesworth et al (England) studied high-resolution computed tomographic scans of the pituitary and hypothalamus of five GHD patients. Definitive enhancing lesions were found in the anterior hypothalamus in each case. Obviously, most cases of pituitary dwarfism arise from hypothalamic damage. These findings are in accord with numerous reports concerning growth-releasing factor (GRF) tests. In the majority of cases, the patient's own GH secretion can be stimulated by exogenous GRF.

Argente et al (France) presented interesting correlations between plasma levels of GRF (by radioimmunoassay) and sexual maturation. At midpuberty, plasma GRF levels increased fivefold in girls but only twofold in boys over prepubertal values. Patients with idiopathic delayed puberty had markedly lower values.

Garnier et al (France) explored the continuing difficulties in determining the cause of short stature. This group investigated hGH secretion in 54 children with growth failure by evaluating nocturnal sleep and GH release to GRF and by performing various pharmacological tests. They concluded that the GRF test does not differentiate among atypical growth disorders.

The final height of 22 patients with hormone deficiencies treated with long-term GH correlated significantly with the midparental height and inversely with the height at onset of therapy, according to a study by Frisch et al (Austria). Eight children had isolated GHD, and 14 suffered from multiple hormone deficiencies. The duration of treatment was 6.6 ± 3 years, and the average GH dose was 9 IU/week. No correlations were found between final height and the standard deviations of chronological age, the chronological age itself, or bone age. Also, no correlation was found with insulin-like growth factor I levels or with GH levels obtained following provocative tests. Patients who had gonadotropin deficiency had a better prognosis with respect to height than those with idiopathic GHD.

The Henning Andersen Prize for the best paper was awarded to Drs. Maes, Amand, and Ketelslegers (Belgium). They fed rats a protein-poor diet for one week. The capacity of the liver membrane to bind GH, the affinity constants, and the basal somatomedin-C (Sm-C) levels were similar in this group of rats and controls. However, in the protein-deprived rats the increase in Sm-C levels after GH stimulation was only one third that of controls. These investigators concluded that in rats, protein malnutrition induces a GH postreceptor defect.

Letter From the Editor

Dear Colleague:

Welcome to the third year of publication of *Growth, Genetics, and Hormones*. The Editorial Board has worked industriously to provide you with updated summaries of topics of interest to pediatric endocrinologists and geneticists and to provide particularly pertinent abstracts from the literature. We have especially enjoyed providing editorial comments on the abstracts and summaries of meetings we have attended.

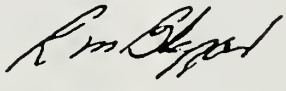
The first issue of Volume 3 has departed somewhat from our usual format. We thought that you might enjoy a historical perspective of Dr. Lawson Wilkins, the pioneer in pediatric endocrinology and, in many respects, in genetics as well. Should your response to this presentation be positive, we will consider presenting further historical perspectives on Dr. David Smith, the Lawson Wilkins Pediatric Endocrine Society, and others in the future.

The second issue of Volume 3 will be devoted in large part to Turner's syndome. Dr. Judith Hall will contribute a major review article and discuss many aspects of Turner's syndrome in both children and adults. There will also be an update on constitutional delayed growth and adolescence by Dr. Jürgen Bierich. An article regarding antibodies against growth hormone will be included. The author will be Dr. Louis Underwood.

The third issue will include an article on basic genetic concepts and chromosome linkage. This superlative presentation by Dr.Thaddeus Kelly provides a wealth of information for those who do not specialize in genetics but wish to deepen their understanding of the subject. We encourage you to set aside a few hours for studious review of Dr. Kelly's article; it will be well worth your time and professional interest.

The articles for the fourth issue of Volume 3 have not yet been chosen. The members of the Editorial Board encourage you to send to us your suggestions for future issues. Our goal this year is to highlight the most recent information available and to address your educational needs in the fields of growth, genetics, and hormones. We extend our best wishes for the coming year.

For the Editorial Board,



Robert M. Blizzard, M.D.
Chairman

Contiguous Gene Syndromes: A Component of Recognizable Syndromes

There are now seven disorders in humans in which some patients with the disorder have visible chromosomal abnormalities and others do not. The conditions in which visible chromosomal deletions are sometimes seen include Prader-Willi syndrome, in which approximately half of the patients have deletions at 15q11; DiGeorge's syndrome, in which about 5% of patients have deletions at 22q11; Langer-Giedion syndrome (trichorhino-phalangeal syndrome type II), in which 80% of the patients have deletion at 8q24; Miller-Dieker syndrome, in which approximately 90% of patients have deletion at 17p13; retinoblastoma, in which 5% of patients have deletion at 13q14; the triad of Wilms' tumor, aniridia, and genitourinary tract malformation, in which about 95% of patients have deletion at 11p13; and the Beckwith-Wiedemann syndrome, in which 5% of patients have duplication of distal 11p. Patients with any of these conditions should have chromosome studies done to establish whether or not the cytogenetic abnormality is present. Frequently, both blood lymphocytes and fibroblasts need to be studied.

These syndromes are particularly interesting, since it is not at all clear whether a specific gene has been deleted or duplicated by the chromosomal abnormalities associated with the syndrome or whether the syndrome is produced by abnormalities in and interactions between a set of genes. The sizes of chromosomal abnormalities are quite variable among patients who are clinically very similar. These seven conditions represent a new category of disorders in which visible chromosomal changes may be seen.

Schmickel RD. *J Pediatr* 1986;109: 231-241.

Editor's comment—*As we learn more about molecular genetics and single gene mutations, we realize that many mutations are actually deletions of genes or parts of genes. Thus, it is not surprising that the larger the deletion, the more likely that more than one gene is involved in the deletion. However, we are only beginning to realize that specific syndromes may actually be the products of multiple gene deletions. The interesting point among the cases reported so far is that in no condition is there uniformity as to the absence of visible chromosome material in all cases of the condition. Thus, we cannot equate the syndrome per se to chromosome deletion. It is not at all clear at this time what the relationship of the deletion is to the production of the abnormality. Also interesting is that two of the conditions, the Beckwith-Wiedemann and Prader-Willi syndromes, have overgrowth, while three of the conditions have cancerous overgrowth. Thus, the gene(s) involved is (are) altered in such a way as to upset normal growth mechanisms. This certainly is an interesting group of diseases, and the etiologies will become clearer as progress is made in molecular genetics.*

The McCune-Albright Syndrome: A Lethal Gene Surviving by Mosaicism

The etiology of this disease is unknown.There is no evidence of a hereditary basis, since there is no convincing report of a family incidence except one report involving monozygotic twins. Dr. R. Happle of Germany theorizes that the syndrome is caused by a gene that is dominant and lethal, unless the effect is diluted through mosaicism. He postulates that patients with this syndrome are mosaics for the gene.

Happle states that pigmented lesions often show a unilateral arrangement, strictly respecting the ventral midline. He also states that one important fact has been overlooked previously: Based on his observation of a patient, plus a review of the literature, pigmentation in this syndrome follows the lines of Blaschko. As a general rule, nevoid skin lesions following the lines of Blaschko result from the dorso-ventral outgrowth of two different populations of cells during early embryogenesis, thus reflecting mosaicism. Since patients suffering from the McCune-Albright syndrome have this cutaneous pattern for their pigmentation, Happle believes it is likely that these patients have two different clones of cells.

Happle postulates that if the gene for McCune-Albright syndrome were merely functional, one would expect that the syndrome would be inherited. However, all cases are sporadic. This can best be explained by the presence and action of a "dominant" lethal gene that kills the embryo during its development. Patients with this gene could survive only if they were mosaics. If this thesis is correct, the mosaic state could be produced either by a gametic half chromatid mutation or by an early somatic mutation. Unilateral or even more circumscribed involvement would result from a mutation occurring at a later time in embryogenesis.

This theory could explain the scattered and asymmetric distribution of bone lesions. It could explain the protean variability of endocrine disturbances. It could also explain the occurrence of incomplete forms of the syndrome, which would be attributed to a minor proportion of mutant cells within the total cell population. The mosaicism resulting from a gametic half chromatid mutation could also explain the simultaneous occurrence observed in a set of monozygotic twins.

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McCune-Albright Syndrome

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Happle concluded that both males and females with the McCune-Albright syndrome are able to produce offspring. For the practical purpose of genetic counseling, the action of a lethal gene would explain why the risk of recurrence is not increased for the patient's siblings and children. The concept would imply that affected women should have an increased rate of spontaneous abortions. The loss of the zygote, however, might occur at the time of implantation and thus remain unnoticed. Special attention will be given to this question in further clinical studies.

Happle R. *Clinical Genetics* 1986; 29:321-324.

Editor's comment—*This is a fascinating postulate. Happle has previously written about mosaicism and the occurrence of certain dermatological lesions that follow the lines of Blaschko. In an article in* Human Genetics *(1985; 70:200-206) which is entitled "Lyonization and the lines of Blaschko," Happle writes that the lines of Blaschko represent a nonrandom developmental pattern of the skin fundamentally differing from the system of dermatomes. He found a causal relationship between lyonization and the lines of Blaschko to be quite obvious. Apparently, in women affected with X-linked skin disorders, the lines of Blaschko visualize the clonal proliferation of two functionally different populations of cells during embryogenesis. The lesions arise probably from cells in which the X chromosome that bears the mutation is the active one, whereas the normal skin develops from cells in which the normal cell is active.*

The Origin of 45,XO Males

Maleness in association with a 45,XO karyotype is a very rare and hitherto unexplained condition, previously described in fewer than ten patients. Most individuals with this karyotype develop as phenotypic females with Turner's syndrome. How maleness arises in the XO males, who have invariably been sterile, has been unclear until the study of De la Chapelle et al.[1]

Two 45,XO males were studied. Both had third-degree hypospadias and cryptorchidism, but two testes were found in each. One testis, which was examined in the first patient at 6 to 7 years of age, was "normal." In the second patient, both testes were on the left side and shared a common vas deferens. Both patients were below the second percentile in height; there was no significant mental retardation. There were characteristics suggestive of Turner's syndrome in the first patient, including a mild pterygium colli, highly arched palate, shield-shaped chest, laterally located mamillae, clinodactyly of the fifth fingers, deep-set nails, and coarctation of the aorta.

Both parents of both patients were cytogenetically normal. Four blood cultures and one fibroblast culture from the first patient had only 45,XO mitotic cells. However, a buccal smear revealed 15 of 1,000 cells had fluorescent spots that were believed to reflect the presence of a Y chromosome or a Y chromatin body. A repeat buccal smear several years later showed that 5% of the cells had a fluorescein-staining body. A repeat skin fibroblast culture showed five of 186 cells with a 46,XY karyotype. Another repeat culture yielded similar findings, and these cultures were used for studies to identify Y-DNA sequences. Repeat cultures in the second patient were negative and repeat buccal smears were negative for fluorescein-staining material.

By using restriction digestion, agarose electrophoresis, gel transfer, and hybridization with radiolabeled, cloned DNA probes, it was possible to demonstrate a small amount of Y-DNA material (3%) from the cells of the first patient. There was no demonstrable Y-DNA material from the cultures of the second patient. Using refined techniques, it was possible to show that the X chromosomes of both patients originated from their mothers.

A 45,XO male might be a 45,X/46,XY mosaic, in whom the XY line is rare or has been eliminated altogether, at least in some tissues. The first patient appears to fall into this category. The Y chromosome present in 3% of fibroblasts was structurally normal. Extensive cytogenetic and DNA studies in the second patient produced no evidence of Y chromosomal material, even in a minority of cells. Current techniques used in this study permit identification of a normal Y chromosome in as few as one in 10,000 cells. Therefore, mosaicism of a normally structured Y chromosome is unlikely in this patient. However, some of the identifiable fragments of the Y are located principally in the distal Yq and, thus, would be of little use in detecting mosaicism involving an abnormal Y chromosome lacking that region. The DNA hybridization studies alone, then, cannot argue against low-grade mosaicism for a structurally abnormal Y chromosome in the second patient. There is also the possibility that a Y-bearing cell line existed in tissues other than those that were sampled or existed in the fetal stage, but later eliminated.

Maleness in 46,XX males may be explained by the X–Y interchange hypothesis, which states that the Xq–bearing position of the father's X chromosome can be replaced by a testicular-determining portion of his Y chromosome, which hypothetically might occur as a result of interchange of genetic material between the X and Y

chromosomes at paternal meiosis. Consistent with this hypothesis is the identification of certain single-copy, Y-specific DNA sequences that were detected in 12 of 19 XX males who were tested by Page et al.[2] Thus, it appears that X–Y interchange can account for many cases of XX maleness. In both cases of XO maleness reported here, however, there is no evidence for genetic transfer of Y material. The X chromosome in both patients was of maternal origin. Mosaicism may have accounted for the differentiation of the genitalia along male lines in the first patient. In the second patient, the absence of a certain single-copy Y-DNA sequence argues against, but cannot exclude, the presence of the testis-determining portion of the Y chromosome.

1. De la Chapelle A, Page C, Brown L, et al. *Am J Hum Genet* 1986;38:330-340.
2. Page C et al. *Am J Hum Genet* 1986;38:109.

Editor's comment—*These patients, although extremely rare, remind us how much we do not know about normal sexual differentiation. For several years, attention focused on the presence of H–Y antigen to explain differentiation of the normal male fetus along male lines. We now have learned that H–Y antigen is probably of no consequence, even if it exists. The concept that Y chromosomal material is necessary for differentiation of the gonad along male lines has been defied by the second patient, although mosaicism may have been present at some time early in his life.*

*Of importance to clinicians and investigators is the concept that cultures of fibroblasts from the gonads are exceedingly important when karyotypes from lymphocytes or skin fibroblasts confuse our interpretation of what has taken place. Several years ago, Goldstein et al (*J Pediatr *1977;90: 604) described a short female with stigmata suggestive of Turner's syndrome and gonadal agenesis. Cultures of skin fibroblasts and lymphocytes revealed a 46,XX karyotype; when grown from biopsies of the gonadal streaks, fibroblasts had a karyotype of 45,XO. Possibly, if fibroblasts had been grown from the testes of the two 45,XO males, Y chromosomal material would have been more readily identifiable.*

Treatment of Duchenne's Muscular Dystrophy With Growth Hormone Inhibitors

Although major advances are being made in isolating the gene for Duchenne's muscular dystrophy, the basic mechanism of this disorder is still unknown. It may be several years before the function of the gene is understood. In the meantime, the disease continues its relentless deterioration process in affected males.

An interesting clinical observation reported by Zatz et al five years ago has led to some very important therapeutic implications. The report was about a boy with Duchenne's muscular dystrophy who also had growth hormone deficiency (GHD) and a relatively benign course. When compared with other affected individuals in his family, he was very much less severely affected. For this reason, Zatz et al undertook to utilize growth hormone (GH) antagonists in the treatment of Duchenne's muscular dystrophy. Specifically, she treated one of two identical twins with the disease in a double-blind controlled study. The treatment involved the use of the GH antagonist mazindol. After one year of the therapeutic trial, the code was broken and the identical twin boys were compared. The twin being treated by GH antagonist was significantly less severely affected after a year of therapy than his brother, who had typical progression of his disease.

In the same issue of the *American Journal of Medical Genetics,* Zatz et al report the follow-up on the patient observed five years ago. The boy is still alive and functional at 18 years of age, while the other affected members of his family had already died or been non-ambulatory by the same age.

Zatz M, Betti RTB, Frota-Pessoa O. *Am J Med Gen* 1986;24:549-566, 567-572.

Editor's comment—*Duchenne's muscular dystrophy is one of the most common and distressing of single gene disorders. The basic mechanism of the disease has eluded definition, and until this report of Zatz et al, there has been no real hope for interrupting the progressive deterioration of affected boys. Advances in genetics are frequently made by experiments of nature and observation; the insight to appreciate that the boy who was affected with GHD was actually doing "well" with regard to his Duchenne's muscular dystrophy was extremely important. The observation that the identical twin who was treated with GH antagonist is significantly better than his non-treated twin raises the possibility that cell growth may have some role in Duchenne's muscular dystrophy. It may well be that smaller cells somehow do better and survive longer in the presence of the Duchenne's muscular dystrophy gene. It may be that boys with Duchenne's muscular dystrophy begin to do poorly with the increased turnover of cells and that GHs stimulate this turnover. Whatever the case, this important clinical observation may well lead to immediate treatment for Duchenne's muscular dystrophy. In addition, it is interesting to speculate whether GH antagonist may offer potential therapy in other degenerative diseases.*

Retinoic Acid Embryopathy

Retinoic acid is a derivative of vitamin A and is presently used effectively to treat a variety of skin disorders, including serious acne. It has long been recognized from animal studies that retinoic acid and isotretinoic acid are teratogens, but when isotretinoin came into general use for cystic acne in human patients, many pregnant women were exposed to it. A "retinoic acid embryopathy syndrome" is now recognized among babies whose mothers took vitamin A derivative during pregnancy. Features of the syndrome include abnormalities of the cranium and face, central nervous system, heart, and thymus. The authors point out that it is difficult to conduct a proper prospective study because most women on treatment elect termination of pregnancy. However, among 36 pregnancies studied prospectively, eight resulted in spontaneous abortions, 23 in normal infants at birth, and five in malformed infants.

This paper reports 21 malformed infants with a characteristic pattern of malformations. Cranial and facial abnormalities include microtia and anotia, micrognathia, and cleft palate; cardiac anomalies include conotruncal heart defects and aortic arch abnormalities; central nervous system abnormalities include hydrocephalus, fourth-ventricle cyst, holoprosencephaly and microcephaly, as well as major errors in cortical and cerebellar neuronal migration; and thymus abnormalities include ectopia, hypoplasia, and aplasia.

The exact timing and mechanism of teratogenesis are unknown. The authors speculate that exposure to isotretinoin may produce abnormal cephalic-neural-crest-cell activity around the 28th day of gestation. This would imply that early exposure is of greatest concern. Isotretinoin has a short half-life of between 16 to 20 hours. Thus, it would appear that there is no long-term effect of isotretinoin ingestion, and nonpregnant women need not worry about an effect after discontinuing this medication. The exact dose that may produce anomalies has not yet been determined.

The data in this report suggest an increased risk for spontaneous abortions and a risk of about 20% for having a child with obvious congenital anomalies at birth among women who have taken isotretinoic acid early in pregnancy.

Lammer EJ, Chen DT, Hoar RM, et al. *N Engl J Med* 1985;313:837-841.

Editor's comment—*It is quite clear from animal and now human studies that vitamin A and its analogues are teratogenic in humans and cause a characteristic pattern of anomalies. It is extremely important that physicians make this potential side effect clear to women of childbearing age when prescribing isotretinoin or other vitamin A preparations. If a woman has been inadvertently exposed, she must be offered the option of prenatal diagnosis because many of the structural defects can be identified prenatally. Many fetuses exposed to vitamin A derivatives will spontaneously abort. To date, over half the reported children who have been exposed to isotretinoin during the early stages of gestation appear normal at birth. However, long-term follow-up of their intellectual development has not yet been possible.*

Effects of Cyproterone Acetate on Statural Growth in Children With Precocious Puberty

For the treatment of precocious puberty (PP), drugs with three different actions are available: progestational steroids with antigonadotropic activity (eg, medroxyprogesterone acetate); progestins with additional antiandrogenic effects (eg, cyproterone acetate or CPA); and luteinizing-hormone–releasing hormone (LHRH) analogues, which block the pulsatile secretion of the gonadotropins from the hypophysis. With all three types of drugs, it is possible to suppress the sexual development of patients.

Less satisfactory is the effect on longitudinal growth and skeletal maturation. Untreated girls with idiopathic PP usually attain an adult height of between 146 and 154 cm (Thamdrup [1961]; Sigurjonsdottir and Hayles [1968]). Treatment with medroxyprogesterone acetate does not produce an increase in adult height. Opinions concerning CPA are contradictory. In fact, outcome of therapy has been difficult to evaluate, since only predicted heights and no measured heights have been available. LHRH analogues have not been tested for a long enough period for reliable judgment.

In a multicenter study, Sorgo et al recently ascertained the success of long-term administration of CPA in 44 patients with PP, 31 of whom had idiopathic PP. The investigators measured adult height. Twenty patients had received CPA in a dosage of 117 ± 6 mg/m^2/day (group A) and 24 in a dosage of 60.8 ± 2.4 mg/m^2/day (group B); the duration of treatment averaged 4.8 years. The chronologic age (CA) of female patients was 5.45 years at start of treatment and the bone age (BA) was 8.57 years. Thus, BA exceeded CA by 3.12 years. During therapy, height standard deviation scores for chronologic age (SDS_{CA}) dropped from 2.54 to 1.28 in group A, whereas group B showed no significant change. Height SDS_{BA} did not change in either group. The height velocity

scores for CA and BA quickly decreased and reached subnormal values by the second or third year of treatment. At the same time, skeletal maturation expressed by BA/CA fell from very high (2 to 3) to normal values (around 1.0). Thus, after initiation of treatment, no further deterioration or relative height loss occurred. No significant differences between the two groups were found. Also, selecting only the idiopathic cases of PP, no difference in adult height was encountered in the groups: group A measured 153.3 cm, group B 153.4 cm.

Sorgo W, Kiraly E, et al. *Eur J Pediatr* 1985;145.

Editor's comment—*This large study confirms that high-dose and low-dose treatment with CPA does not increase statural growth in patients with idiopathic PP. The results are particularly important because the parameter used was measured, not predicted, final height. This makes a great difference, when compared with the findings of most earlier publications.*

It is critical to mention that investigators should not mix children with idiopathic PP with those who have McCune-Albright syndrome, since most patients with the latter condition do not have increased secretion of gonadotropin. It is not surprising that patients with McCune-Albright syndrome have significantly diminishing relative height during CPA treatment—which is of minor value in this condition.

Patients with idiopathic PP, however, did not have deteriorating growth (final height) prognosis. Predicted and final height did not significantly differ. In our opinion, this may represent a therapeutic success, although a limited one. Observations by Bierich (1980) and Murram et al (1984) predicted that final height gradually diminishes in young children with idiopathic PP who remain untreated.

Levels of Growth-Hormone–Releasing Factor During Growth Hormone Stimulation Tests and During Puberty: Two Reports

Donnadieu and co-workers[1] established an assay for growth-hormone–releasing factor (GRF) and evaluated the concentration in the plasma both in children receiving various stimulation tests for growth hormone (GH) release and in children at various stages of puberty.

This assay measured GRF-40 and GRF-44 equally and required the extraction of 2 ml of plasma. Eight samples collected over a two-hour period from each of three boys varied from 43-73 pg/ml in the first, to 8-22 pg/ml in the second, and to 41-95 pg/ml in the third.

In the first report, these authors found that L-dopa stimulation of GH release is preceded by a significant rise in GRF. In contrast, when ornithine infusion is used as a pharmacological agent to cause GH release, GRF falls. The authors conclude that different mechanisms account for GH release by these two agents.

In the report by Argente and colleagues,[2] basal GRF concentrations were measured in samples from 180 children. These were collected between 8 AM and 10 AM after an overnight fast. Correlations between basal GRF values of children in various stages of puberty and steroid and insulin-like growth factor I (IGF-1) levels were sought by the investigators.

As shown in the Table, basal levels in girls increased progressively during the first four stages of puberty and fell in stage V. Basal levels in boys increased from stage I to stage II and to stage III progressively. The values plateaued during stage IV and then fell in boys with stage V sexual development. The pubertal values in girls were significantly higher than in boys and increased progressively until stage IV, after which they fell markedly. There was no correlation between plasma GRF levels and sex steroids or growth velocity. Positive correlation was found between basal GRF values and IGF-1 values in both sexes.

Fourteen boys with delayed puberty had values of 30.8 ± 7.5 pg/ml. These were comparable to the values found in boys in stage I of puberty.

1. Donnadieu M, Evain-Brion D, Tonon MC, et al. *J Clin Endocrinol Metab* 1985;60:1132.
2. Argente J, Evain-Brion D, Munoz-Villa A, et al. *J Clin Endocrinol Metab* 1986;63:680.

Editor's comment—*These authors are to be commended for developing an assay that permits evaluation of the physiologic role that GRF plays in the secretion of GH. Readers probably will want to follow the literature closely to observe the reporting of further observations pertaining to the role that GRF plays (and does not play) in the normal and abnormal physiology of GH secretion.*

Table: GRF Levels During the Stages of Puberty

	Prepubertal	Early Pubertal	Midpubertal		Late Pubertal
	I	II	III	IV	V + Menses
Girls	30.3 ± 4.3	56.6 ± 6.1	143.7 ± 21.3	176.6 ± 35.7	60.5 ± 6.0
Boys	48.1 ± 5.2	75.9 ± 4.3	103.5 ± 13.8	99.3 ± 9.3	60.6 ± 5.7

Prenatal Diagnosis of Autosomal Dominant Polycystic Kidney Disease With a DNA Probe

Polycystic kidney disease is one of the most common dominantly inherited disorders in man, occurring in about one in 1,000 individuals. Approximately 10% of all cases requiring renal dialysis and kidney transplant have autosomal dominantly inherited polycystic kidney disease of the adult type. Recently, the disorder had been localized to an abnormality of the short arm of chromosome 6, and genetic linkage has been demonstrated to the alpha chain of human hemoglobin and phosphoglycolate phosphatase. With this knowledge, it is possible to diagnose "presymptomatic" carriers; most recently, prenatal diagnosis has been accomplished by DNA analysis of chorionic villus sampling.

The report, which is very straightforward, describes techniques that have been developed in the last few years. It is important, however, for the practitioner to be aware that these sorts of techniques have been developed and that analysis of family members is possible. Linkage can be determined and presymptomatic carriers can be detected, thus permitting prenatal diagnosis.

Reeders ST et al. *Lancet* 1986;7:6.

Editor's comment—*The remarkable advances that have been made in the last few years are very dramatic. Only three years ago, presymptomatic detection of individuals with polycystic kidney disease was not thought to be possible. Now it is possible to diagnose the entity before symptoms occur. Equally important is the fact that prenatal diagnosis during the first trimester using chorionic villus sampling is also possible. This allows prospective parents to make alternative decisions.*

Peroxisomal Disorders: Three Reports

A recent review of peroxisomal disorders has focused attention on them and has allowed their features to be summarized. The list of peroxisomal disorders is increasing with the increased index of suspicion. Thus far, all of the peroxisomal disorders show accumulation of bile acid precursors and very long chain fatty acids, with impaired biosynthesis of plasminogens. In some cases, abnormal peroxisomes can be seen on electron microscopy.

Interestingly, all cases of peroxisomal disorders also have minor congenital anomalies. These include structural abnormalities of the brain due to malmigration of neurons, dysplastic cystic kidneys, retinitis pigmentosa due to dysplasia of the retina, hepatomegaly, deafness, stippled epiphyses, and abnormal facies with high forehead and myopathy. Mental retardation and hypotonia are usually present as well. None of these clinical features are pathognomonic.

The biochemistry of peroxisomal disorders is poorly understood at this time. However, good screening tests of urine, serum, and fibroblasts are beginning to be developed. Presently, Zellweger's syndrome, adrenoleukodystrophy, infantile Refsum's syndrome, infantile Conradi's syndrome, and Leber's disease have been defined as peroxisomal disorders. The index of suspicion for these disorders should be raised when evaluating any child with minor anomalies of the type described above.

The report of pseudo-Zellweger's syndrome by Goldfischer et al[1] indicates that one can have abnormal peroxisomal function in the presence of abundant peroxisomes. The report of Leber's disease by Ek et al[2] described specific changes of macular hyperpigmentation and absence of electroretinographic responses without the other features of Zellweger's syndrome. This finding suggests that any disorder with dysplasia of the retina needs to be considered as a potential peroxisomal disorder. The description of "infantile" Refsum's syndrome by Sargini et al[3] reminds us that the presence of neurosensory deafness and retinitis pigmentosa indicate the possibility of the diagnosis of a peroxisomal disorder. This is particularly true in children with hypotonia and hepatomegaly. Sargini et al found four patients within six months when they began to look for the disorder. This suggests that this may be a relatively common condition.

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Editor's comment—*Peroxisomal disorders are a whole new class of inborn errors of metabolism in which the combination of long chain fatty acid metabolism and congenital developmental anomalies is seen. Although the definition of peroxisomal metabolism is in its infancy, peroxisomal disorders appear to be inborn errors of metabolism in which morphogenesis is affected. This is an exciting new area that will surely allow the description of a whole new set of specific single gene disorders.*

Growth, Genetics, and Hormones - Index 1985/86

Copies of back issues of *Growth, Genetics, and Hormones* are available and will be sent to readers who request them. Simply note the volume and issue number(s) on a postcard (or your letterhead) and mail to Ms. Amy Conovitz, Biomedical Information Corporation, 800 Second Avenue, New York, New York 10017.

MEETING CALENDAR

April 27-30 Annual Meeting of the American Pediatric Society/Society for Pediatric Research. Disneyland Hotel, Anaheim, California. Contact: Debbie Wogenrich, Department of Pediatrics, University of New Mexico, Albuquerque, NM 87131 (505-277-6628)

May 1 Annual Scientific Session, Lawson Wilkins Pediatric Endocrine Society. Disneyland Hotel, Anaheim, California. Contact: Dr. Gilbert August, Department of Endocrinology and Metabolism, Children's Hospital, 111 Michigan Avenue NW, Washington, DC 20010 (202-745-2121)

June 4-12 47th Annual Meeting and Scientific Sessions, American Diabetes Association. Hyatt Regency Hotel, Indianapolis, Indiana. Contact: American Diabetes Association, 1660 Duke Street, Alexandria, VA 22320 (800-232-3472)

June 10-12 69th Annual Meeting, The Endocrine Society. Indianapolis Convention Center, Indianapolis, Indiana. Contact: Nettie Karpin, Executive Director, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-530-9660)

July 19-22 Clinical Genetics Conference. March of Dimes–Birth Defects Foundation and the University of Minnesota, Twin Cities. Radisson Hotel, Minneapolis, Minnesota. Contact: Dr. Robert Gorlin, University of Minnesota School of Dentistry, 515 Delaware Street SE, Minneapolis, MN 55455.

September 28-30 International Congress on Advances in Growth Hormones and Growth Factors Research. Milan, Italy. Contact: Drs. Daniela Cocchi and Vittorio Locatelli, Department of Pharmacology, Chemotherapy, and Toxicology, University of Milan, Via Vanvitelli 32, 20129 Milan, Italy

Growth, Genetics, and Hormones is published under an educational grant from Genentech, Inc.

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800 Second Avenue
New York, NY 10164-0569

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GROWTH
Genetics & Hormones

Vol. 3 No. 2 June 1987

Antibodies to Growth Hormone: Measurement and Meaning

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Some patients develop serum antibodies to growth hormone (GH) during GH therapy. Although these antibodies do not produce immune complex disease, their occurrence causes concern among endocrinologists because they may attenuate the growth-promoting effect of GH therapy in a small number of patients. In this presentation, we will review the factors involved in the production of antibodies to GH, the methods for detecting and quantitating serum GH antibodies, and the relationship between the amount of antibodies measured and the occurrence of growth attenuation.

Causes of GH Antibodies

With insulin and other peptides of animal origin, the lack of identity between the structure of the peptide used therapeutically and the corresponding peptide of the host is one cause for stimulation of the immune response and production of serum antibodies. Intuitively, this should not be the cause for GH antibodies when authentic human growth hormone (hGH) is given to humans. GH preparations used therapeutically (including biosynthetic GH), however, contain some GH with modified molecular structure. These modifications include deamidation, dimerization, proteolytic cleavage, and deletions, which produce forms that may not be secreted normally. In addition to exposure to a foreign peptide, the immune system may be excited to form antibodies when the peptide is presented by an unusual route, the peptide preparation is contaminated with substances that act as adjuvants, or the secondary and tertiary structure of the peptide is altered.

Historically, the occurrence of antibodies to pituitary-derived GH correlated with the quality of the preparation injected. Antibodies were observed in as many as 60% of the hypopituitary children treated with early preparations that contained aggregates of GH and an abundance of contaminating peptides. As purer preparations of monomeric GH came into use, the incidence of antibodies fell to below 10% with some preparations, and growth attenuation due to antibodies was rare. Unlike insulin antibodies that have been shown to be more prone to form in insulin-treated diabetic patients who have certain HLA types, the host factors that predispose to the formation of antibodies to injected GH have not been defined. Exceptions to this are the rare patients who are GH-deficient (type 1A) because of a deletion in the gene encoding for GH. In these patients, formation of a massive quantity of antibodies to GH is common.

Before recombinant DNA–derived human insulin was available, it was widely believed that its use would obviate the formation of antibodies to insulin in diabetics. This, however, was quickly proven *not* to be the case. Likewise, it came as a surprise when treatment with the first preparations of recombinant methionyl GH caused antibodies to form in a significant percentage of patients. Production of GH antibodies declined sharply, however, after improvements in purification procedures for methionyl GH were made and since the introduction of recombinant hGH with no N-terminus methionine. If antibodies are to occur, they usually can be detected early in therapy (by three to six months), regardless of the

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Antibodies To Growth Hormone: Measure and Meaning

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hGH preparation used. Evidence from one laboratory indicates that antibodies may be transient, especially in patients with low levels of binding. Therefore, the frequency of occurrence of antibodies may vary, depending on the frequency and timing of their measurement.

What Needs to Be Done Before Screening for Antibodies

The question of whether a child has GH antibodies arises when he/she fails to grow in response to GH therapy. However, in the list of possible causes of poor responses to GH therapy, antibodies must rank near the bottom. The following questions should be answered before one screens for antibodies: Is the diagnosis of GH deficiency correct? Are the measurements of linear growth and the calculation of growth rate accurate? Has the patient had significant illness during the interval in question, and, if so, could such an illness have impaired the response to treatment? Has the child's nutritional intake been sufficient to support growth? Is the child receiving the prescribed GH dose, and is the hormone being administered properly? Most of these questions can be answered readily. Should they provide no clues, serum should be drawn for assessment of antibodies.

Screening for GH Antibodies

Screening for GH antibodies is accomplished by incubating an aliquot of the patient's serum (the potential source of antibodies) with a small quantity of radiolabeled GH (~10,000 cpm). The incubation is ended by separating the labelled GH that is bound by antibody from the unbound labelled hormone. Binding in patient serum that is more than twice the mean of sera from subjects not treated with GH is usually taken as evidence of the presence of antibodies. It is advisable to confirm that the binding observed is specific for GH by assessing the inhibition of binding of labelled GH by excess unlabelled GH. When antibodies are present, the addition of an excess of unlabelled GH will reduce the binding to values equal to those of control sera.

In the incubation procedure, two features are crucial for adequate screening. First, sufficient serum must be added to detect small amounts of antibody. Second, a reliable method for separating bound from free hormone must be available. The final dilution of serum in the reaction mixture, which contains radioimmunoassay (RIA) buffer, should be 1:20 or less. Of the separation methods available, we prefer to use a gamma globulin precipitant such as polyethylene glycol (PEG) or an anti–human gamma globulin second antibody that is known to precipitate gamma globulin efficiently. We prefer to separate bound from free hormone by precipitating the former with a second antibody, because precipitation with PEG is subject to variability from a number of factors. Less reliable separation methods include chromatoelectrophoresis and dextran-coated charcoal binding of labelled hormone not bound to antibody. With the latter, spurious information is obtained when the antibody-bound labelled hormone separates in the charcoal fraction along with the free hormone.

Measurement of Binding Capacity, Affinity, and Titer

High binding capacity seems to correlate best with the growth-inhibiting effect of GH antibodies. Measurement of binding capacity is accomplished in much the same way one would set up a standard curve in an RIA. Fixed amounts of the test serum and labelled GH are added to a series of tubes containing increased amounts of unlabelled GH (concentration range of 1 to 1000 ng/ml). Following incubation and separation of bound from free hormone, a curve of competition can be derived. From this, the binding capacity can be determined using a Scatchard plot.

While growth attenuation from GH antibodies appears to correlate best with binding capacity, affinity of binding also can be determined from the Scatchard plot and may also be a determinant of the biological importance of GH antibodies. However, the use of affinity measurements has been limited, since these figures are difficult to quantify precisely.

In many of the studies of GH antibodies in GH-treated patients, laboratory assessment has focused on measurements of titers. We believe that determining the highest dilution of serum at which binding can be detected is of minimal value unless it is followed by a measurement of binding capacity. However, clues to the possible importance of GH antibodies in inhibiting growth can be obtained by noting the percentage of tracer bound to antibody in the original screening test. Binding in the range of 20% or less at a serum dilution of 1:10 is not usually associated with high binding capacity or inhibition of growth. On the other hand, if binding is above 50% on the initial screen, the binding capacity and the titers probably will be high, and one should be concerned that the antibodies might interfere with the bioavailability of injected GH. In our experience, binding capacities of less than 5 mg/l of bound GH in the patient's serum are not associated with growth attenuation. Values of 10 mg/l or greater are usually found in patients who have impaired responses to exogenous GH. The relationship between the time that the serum sample is drawn for antibodies and GH therapy must be considered in the interpretation of binding capacity. Lack of antigenic stimulation, as during cessation of therapy, results in a decrease in binding capacity. Also, a recent injection of GH may saturate the antibody, thereby lowering apparent binding capacity.

GH Antibodies and Attenuation of Growth

Serum GH antibodies almost certainly exert their biological effect by binding injected hormone,

thereby limiting the hormone's availability to tissues. Whether binding is great enough to have biological significance is probably determined by the abundance of antibody in the serum, the affinity of binding of the hormone by antibody, and the competition between binding to antibody and to GH receptors on cells. Supporting this is the observation that large amounts of antibody (more than 10 mg/l) slow the removal of GH from the circulation during the phase of disappearance that is ordinarily determined by the uptake of GH by tissues.

Detection of GH antibodies in the serum of a patient being treated with GH does not require that the therapeutic plan be changed unless the growth response is attenuated. In the case of attenuated growth in association with a high serum binding capacity for GH, it may be advisable to change from one GH preparation to another. In the past, when a variety of pituitary GH preparations were available, changing from one preparation to another often resulted in a resumption of growth and a fall in antibody binding capacity. Alternatively, it may be possible to overcome the GH resistance induced by antibodies by increasing the dose of GH. The latter approach, however, has not been attempted to date. Hopefully, as recombinant hGH preparations are improved, inhibition of the growth response by antibodies will not occur except in those patients with hGH deficiency secondary to gene deletion.

Additional Reading

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Letter From the Editor

Dear Reader:

This issue contains three excellent reviews of pertinent topics to geneticists and endocrinologists. The article by Drs. Underwood and Moore provides a fresh perspective for endocrinologists and geneticists who have not yet had the chance to become acquainted with the techniques used to detect serum antibodies to hormonal peptides. The article is also very timely, since there has been much discussion recently regarding the importance of antibodies to growth hormone (GH) in patients treated with native GH, methionyl-GH, and met-less GH. As Drs. Underwood and Moore point out, there is little significance to antibodies that are present *unless* there is significantly high binding capacity (>5 mg/l).

Dr. Hall's review of Turner syndrome is comprehensive in all respects. The variability of the pathology of this syndrome never ceases to amaze me. We see patients with an XO karyotype who have extensive dysmorphology but who, on occasion, have normal estrogen production. We see others with the same karyotype who have minimal dysmorphology, but who may have complete absence of ovarian tissue. The etiology of the short stature is still an enigma. Many of us postulate that the short stature is attributable to a presumed chondrodystrophy but, if so, what kind? There are no consistent radiological findings of the skeleton, and no abnormality of body proportions to permit us to deduce this. Turner syndrome should challenge also the molecular geneticists. How do the genes on the X and Y chromosomes affect growth?

Constitutional delay of growth and adolescence is the most frequent type of short stature seen by clinical endocrinologists in boys. Dr. Bierich reviews the explicit signs and the vagaries of making this diagnosis. We would all agree that it is often difficult to differentiate between partial growth hormone deficiency, constitutional delayed growth and adolescence, and even psychosocial short stature. In his article, Dr. Bierich presents his current thoughts on constitutional delay of growth, an entity to which he has devoted considerable time, effort, and concern.

The Editorial Board hopes you will find these articles informative, helpful, and provocative. We invite you to write us about them. We are pleased to offer *Growth, Genetics, and Hormones* as a forum of communication between the Board and our readers.

For the Editorial Board.

Robert M. Blizzard, M.D.
Chairman of the Editorial Board

Turner Syndrome: An Update

Judith G. Hall, M.D.
Associate Editor
Growth, Genetics, and Hormones

In 1938, Henry Turner described a syndrome of sexual infantilism, webbed neck, cubitus valgus, and short stature in a group of females.[1] Subsequently, gonadal dysgenesis was recognized as a part of this syndrome. It was not until 1959, however, that the chromosomal abnormalities of the syndrome described by Turner were defined.[2] The presence of only one normal functioning X chromosome is characteristic; the other sex chromosome may be missing or have been deleted, or it may be present in a mosaic form. Isochromosomes, which are duplications of the short or long arm of one of the X chromosomes, are also seen. Although, in the past, the buccal smear sometimes was helpful in establishing the diagnosis of Turner syndrome, cytogenetic studies are necessary to confirm it.[3]

Diagnosis and Karyotype

The minimal diagnostic criterion for Turner syndrome is an abnormal karyotype in at least one tissue in which a portion or all of the X chromosomes is missing. There have been reports of patients with 46,XX karyotypes of lymphocytes and fibroblasts from skin, but who have abnormal karyotypes of cells in the gonads. In contrast, there are patients who have abnormal karyotypes in the lymphocytes and fibroblasts, but who probably have normal karyotypes in the ovarian tissue. These are the patients who may be able to become pregnant.

Individuals with 45,X/46,XY karyotypes may present with the typical stigmata of Turner syndrome, or they may present as males with insignificant hypospadias. Identifying 45,X/46,XY, if present, is essential because malignant degeneration (gonadoblastomas) may occur in the streak gonads. Any patient diagnosed as having Turner syndrome who has not been karyotyped in the past should have karyotype analysis performed to rule out the presence of a Y chromosome. In the future, the presence of Y-bearing cells in 45,X Turner syndrome patients may also be detected by monoclonal antibodies to the Y chromosome or by DNA probes to the Y chromosome.

Turner syndrome should be considered in a female infant with lymphedema or in any female with short stature, primary or secondary amenorrhea, or both. Many patients have minimal dysmorphological features, and there is no single pathognomonic clinical feature that clinches the diagnosis.

Attempts to correlate the types of X chromosome anomalies in specific individuals or in groups of individuals according to their phenotypic findings has been of limited success.[4] Genes involved in gonadal function in both the proximal part of the short arm of the X and distal part of the long arm of the X are believed to exist, while the genes for other somatic features must be distributed along the length of the short arm and the middle section of the long arm of the X. There is a rough correlation between the absence of the short arm of the X chromosome and the typical clinical features of Turner syndrome. These features include broad chest, hypoplastic nipples, prominent ears, webbing of the neck, low hairline, high palate, short fourth metacarpal, cutaneous valgus, hypoplastic nails, multiple pigmented nevi, structural anomalies of the kidneys, coarctation of the aorta, and hearing impairment.

One in 2,500 live-born females has Turner syndrome. However, 98% of fetuses with a missing sex chromosome are aborted spontaneously. Typically, 45,X abortuses have a huge cystic hygroma and generalized edema. It is important to do a karyotype on cells from abortuses suspected of having Turner syndrome, since this syndrome does not carry a recurrent risk (of affecting future offspring), but many other causes of fetal hydrops do.

Infants born to the few women with Turner syndrome who are capable of conceiving are more likely to have a chromosomal abnormality (sex chromosomal and autosomal aneuploidies).[5] Advanced maternal age does not appear to be a risk factor for having an infant with Turner syndrome. The paternally derived X chromosome is more likely to be the absent X, but the reasons for this are obscure.

Prior to 12 weeks of gestation, the ovaries in a 45,X fetus appear normal histologically. At that time, the number of primordial germ cells is normal, but the number of follicle cells per oocyte decreases thereafter. The oocytes continue to degenerate; by birth there are few, if any, left, and fibrous streaks replace the ovarian tissue. Two normal X chromosomes are necessary for the follicles to be maintained.

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Growth, Genetics, and Hormones is published by Biomedical Information Corporation under an educational grant from Genentech, Inc. The information in this publication reflects the views of the editors and does not necessarily reflect the opinions of the sponsor or the publisher.

Structural Abnormalities and Other Malformations

Structural or positional abnormalities of the kidneys occur in approximately 60% of patients with Turner syndrome. These abnormalities rarely cause renal malfunction, although recurrent urinary tract infections may occur. Double collecting systems or the absence of a kidney occurs in 20% and malrotation in 15%. An ultrasound of the abdomen is recommended to determine the structure of the kidneys and collecting system. Regular screening for urinary tract infection is indicated in those patients with anomalies.

Lymphedema occurs in approximately one third of the patients. It is caused by congenital hypoplasia, late maturation, and delayed canalization of the lymph channels *in utero*. Persistence of embryonic lymph sacs *in utero* results in severe lymphedema, particularly in the neck area. By birth or shortly thereafter, the cystic hygroma usually recedes, leaving folds of skin and webbing in the neck and a low nuchal hairline. Peripheral edema also decreases during childhood. However, edema may again become a problem when estrogen therapy is begun. Salt restriction and "support" hose may be helpful.

Congenital heart malformations are frequent and all patients with Turner syndrome should have ultrasound and echocardiogram studies of their hearts performed. Coarctation of the aorta occurs in 15% to 30% of patients, but it is often mild. Ectopia cordis and hypoplastic left heart occur rarely. Whenever these two rare cardiovascular anomalies are seen in females, chromosome studies are indicated. Pulmonary stenosis occurs, but it is seen more often in the chromosomally normal Noonan's syndrome, which has a somewhat similar phenotype. Bicuspid aortic valves are seen in approximately one third of patients.[6] Such patients should receive prophylactic antibiotics prior to dental work or surgery to avoid endocarditis. Aneurysm and dissection of the aorta also have been reported in Turner syndrome.[7]

Various other vascular malformations, including intestinal telangiectasia, hemangiomas, lymphangiectasia, and venous ectasias, are occasionally seen in patients with Turner syndrome. Although the malformations are relatively infrequent, they can cause considerable distress. Multiple renal arteries are seen in approximately 90% of patients. No correlation has been made between the extrarenal arteries and hypertension, renal artery fibromuscular hypoplasia, or structural renal anomalies.

Other Conditions Associated With Turner Syndrome

Hypertension occurs frequently in Turner syndrome, even when patients with coarctation and renal anomalies are treated or excluded. Hypertension in Turner syndrome is often idiopathic, is often associated with obesity, and responds favorably to weight reduction.

Autoimmune disease of the thyroid and of the bowel occur. There is a significantly increased incidence of thyroid antibodies, and hyperthyroidism or hypothyroidism can occur. Patients with Turner syndrome need to be screened annually for thyroid disease and examined for autoantibodies or elevated levels of thyroid-stimulating hormone or both.[8]

Regional enteritis and ulcerative colitis are also increased in incidence. Patients who have an isochromosome of the long arm seem to be particularly susceptible to inflammatory bowel disease.[9]

Diabetes mellitus in women with Turner syndrome occurs more frequently than usual. An impaired serum glucose response to an oral glucose load is seen in 25% to 60% of adults with Turner syndrome, but only a few have overt clinical diabetes.[10] Islet cell antibodies are absent in this group of patients. These women have type II diabetes resulting from glucose intolerance, not an autoimmune type of diabetes.

Patients with Turner syndrome run a high risk for tumors of the reproductive system. The risk for gonadoblastoma in 45,X/46,XY individuals increases substantially after the age of 10, with the incidence reaching 25% or more after the age of 30.[11] Ideally, 45,X/46,XY patients should have their streak gonads removed prior to starting school. Both streaks should be removed, since the risk for bilateral tumors is high. Isolated case reports of dysgerminomas, seminomas, and teratomas in these individuals have been recorded.

A variety of other tumors has been described, including chronic myelogenous leukemia, virilizing hilus cell tumors, basal cell carcinomas, eosinophilic adenomas, thymomas, neural crest-derived tumors, and pancreatic growth-hormone-releasing hormone tumors. Theoretically, the risk for malignant degeneration secondary to ulcerative colitis is also increased, although this has not yet been reported.

Skeletal Abnormalities

The skeletal changes associated with Turner syndrome are diverse. These changes, which are sometimes helpful in making a diagnosis, include short fourth metacarpal bones, cubitus valgus, midfacial hypoplasia, Madelung's deformity, increasing angulation of the carpal bones, pes cavus, irregular tibial metaphyses, Schmorl's nodules of the vertebrae, and a somewhat android configuration of the pelvis.

Scoliosis and lack of lumbar lordosis occur fairly frequently. Patients should be observed carefully to detect early curvature of the spine when estrogen therapy is begun. Congenital dislocation of the knees and hips is also seen.

Osteoporosis is said to occur with increased frequency and at an early age because of the radiolucency of the bones, the coarse trabecular patterns, the decreased cortical width, and the decreased bone mineral content. These findings, which are common, do not appear to worsen with age or change significantly with

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estrogen therapy. Patients with Turner syndrome do not have an increased number of fractures or collapsed vertebrae. Thus, it is not clear whether or not osteoporosis occurs more frequently in older women with Turner syndrome than it does in the general population.

A triangular face, down-slanting palpebral fissures, epicanthal folds, ptosis, a broad and short neck often with webbing and a low hairline, mid-facial hypoplasia with undergrowth of the maxilla, deepening of the posterior cranial fossa, and a small mandible with widely spaced mandibular rami characterize the craniofacies. High arched palates often cause feeding problems during the first year of life. Recurrent otitis media is a problem in infancy and childhood and is related to anatomic alterations at the base of the skull that change the angle of the eustachian tube, with the result that drainage from the middle ear is poor. The incidence of hearing impairment in adults with Turner syndrome is high, and chronic middle ear disease appears to be the etiology.

Keloid formation occurs frequently in patients with Turner syndrome. Other dermatological features include abnormal dermatoglyphics, with a large number of whorls on the tips of the fingers and a high percentage of distal triradii. These changes seem to be related to the edema that occurs early in embryonic development. Small, hypoplastic convex or concave fingernails and upturned toenails are also seen frequently.

Pigmented nevi are common and tend to appear late in childhood. Malignant degeneration of these nevi is not a problem.

Mental Function

Although early reports indicated a high incidence of mental retardation among patients with Turner syndrome, this has not turned out to be the case. If a patient proves to have true mental retardation, then the possibility of autosomal chromosome abnormalities should be evaluated and a careful investigation conducted for other causes of the mental retardation.

Girls with Turner syndrome are more likely to have specific problems with conceptualization of spatial relations and numerical identification.[12] Full-scale I.Q. testing reveals that the total I.Q. of Turner syndrome patients is usually average or above average. However, there is often a deficiency in perceptual motor organization or in fine motor execution. Therefore, the nonverbal I.Q. is significantly lower than the verbal I.Q. Learning disabilities in girls with Turner syndrome are currently being studied in greater detail. Arrangements for tutoring and special training programs may have to be made with the child's school if she is having difficulty with mathematics, history, or geography.

The personalities of girls with Turner syndrome are quite varied. Inertia to emotional arousal, high capacity to deal with stress, and strong traditional femininity are described. These girls tend to be isolated from others as they proceed through adolescence. Every effort should be made to enhance growth and sexual development before these girls "isolate" themselves because of sexual infantilism and short stature.

Growth Retardation

Growth curves for patients with Turner syndrome are now readily available through Genentech, Inc. The average adult height achieved by patients with the syndrome is 145 cm, which is the 50th percentile. The heights at the 10th and 90th percentiles are 138 cm and 152 cm, respectively. It should be noted that a significant number of these patients do not fall behind in their growth curves until they are 4, 5, or 6 years of age. Thus, a positive diagnosis of Turner syndrome cannot be ruled out on the basis of a normal growth rate in early childhood.

A report by Ross et al[13] suggested that patients with Turner syndrome may have growth hormone deficiency (GHD). The mean integrated concentrations of growth hormone (GH) over a 24 hour period were similar in Turner syndrome patients and normal girls 8 years of age and younger (4.6 ± 0.7 ng/ml *v* 2.9 ± 0.2 ng/ml) and not statistically different from the 2.5 ng/ml mean value observed in Turner syndrome patients 9 to 17 years of age. However, normal subjects between 9 and 17 years of age had values of 5.7 ± 0.8 ng/ml. The somatomedin-C (Sm-C) determinations were significantly decreased in 6- to 12-year-old girls with Turner syndrome, in comparison with those in normal girls matched for chronological and bone age. Although the authors concluded that a relative GHD in pubertal patients may contribute to their adult short stature, a more simple explanation for the higher integrated GH values during puberty in normal adolescents may be the presence of sex steroids, since these seem to be correlated with the normal increase in Sm-C levels seen at adolescence.

Treatment for Short Stature

Treatment for the short stature associated with Turner syndrome has included low-dose estrogen, oxandrolone (Anavar), GH, and a combination of GH and oxandrolone.[14] The growth rates after the use of oxandrolone (0.125 mg/kg/day) or GH (0.125 mg/kg 3 times a week) increased from 4.3 cm/year to 7.9 cm/year and 6.6 cm/year, respectively, over a one-year period in one series of patients. The combination of these two agents increased the mean growth rate to 9.8 cm/year. The Food and Drug Administration, however, has not yet approved GH for use in patients with Turner syndrome, and these study findings should be considered preliminary. Also, it is not known whether the use of either of these agents increases growth velocity only or ultimate height as well. Extended studies are required to determine whether ultimate height is increased. The use of oxandrolone is not recommended if the pa-

tient's bone age is less than 9 years because of the possibility of inappropriate acceleration of skeletal maturation in relation to the height acceleration.

The use of low-dose estrogen (100 ng/kg/day) has been advocated on the basis of short-term studies, which reported that this increases growth velocity—at least of the tibia and ulna. These studies have not been carried out long term, and it is still equivocal whether low-dose estrogen therapy has a growth-promoting effect in Turner syndrome.

Summary

Turner syndrome occurs in variable forms and should be suspected in short females regardless of associations of dysmorphology characteristic of Turner syndrome.[15] Chromosomal karyotypes are essential for the diagnosis. Physicians should be aware of the complications that occur in patients with Turner syndrome and should anticipate them, so the consequences that result will be minimal. Treatment should be directed towards increasing the height. Preliminary studies indicate that GH plus oxandrolone may be helpful in increasing growth velocity, although it is unknown whether this treatment increases ultimate height. The action of GH, if favorable, probably reflects a pharmacological effect and does not reflect GHD as such.

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Special Report: First International Conference on Achondroplasia—November 17-21, 1986, Rome, Italy

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Associate Editor
Growth, Genetics, and Hormones

This conference was held to review the international experience with some of the new methods that have become available to treat achondroplasia. These included leg lengthening, enlarging the foramen magnum, and prevention of kyphosis. A number of other areas were also explored, including genetics and natural history, psychosocial adjustment, lay support group organizations, neurologic complications, and basic biological research.

Among the most exciting reports were those describing leg-lengthening operations. Major progress has been made over the last three to five years in reducing the complications of leg-lengthening procedures by using percutaneous surgery with external fixators. Previous attempts at leg lengthening were complicated by infection and nonunion. However, presently available techniques include innovations by Russian, Italian, and Spanish investigators that have led to a marked decrease in severe complications and a marked improvement in the actual amount of lengthening achieved. On average, a remarkable 30 cm of additional growth has been achieved in the lower limbs. The actual incidence of such complications as nerve compression, joint stiffness, and lack of full range of motion are not yet known. However, the advantages of the new technique are short hospitalization and mobility during the procedures. In addition, some of the other problems associated with achondroplasia—such as bowing of the legs, abnormal joint angles, lumbar lordosis, and lack of range of motion of the hips—are significantly alleviated by the procedures.

Very few data from basic science investigations are available as yet, but the results presented at the conference were dramatic: The leg-lengthening procedure is a potential therapy for patients with disproportionately short stature. If successful, there is no reason to think the procedure would not benefit patients with other types of dwarfing conditions. In addition, it is proposed that leg lengthening might be accomplished after children are fully grown, although the ideal age may be 14 to 16 years. It is quite clear that older individuals can also benefit from this type of procedure.

In recent years, it has been shown that hormonal therapy has been beneficial in patients whose short stature is due to a variety of etiologies. Since the chondrodysplasias are not among these, it is therefore exciting to learn about the development of an orthopedic procedure that may be an appropriate mode of therapy.

Special Report: The Western Society for Pediatric Research Meetings—February 3-6, 1987, Carmel, California

Judith Hall, M.D.
Associate Editor
Growth, Genetics, and Hormones

Many excellent papers of interest to endocrinologists and geneticists were presented at the meetings of the Western Research Society. Among them was one by Dr. Ray White, who reported that the order of linkage on chromosome 7 for cystic fibrosis is met-CF-J3111. Dr. White also pointed out that the crossover ratios for different segments of different parts of different chromosomes are different in males and females. There is no consistent pattern, and each arm and arm segment of different chromosomes is being recognized to give markedly different crossover rates.

Dr. Judson Van Wyk delivered the Stanley Wright Memorial Lecture. He discussed peptide growth factors and indicated that there may be fewer peptide growth factors than previously thought, because any given growth factor may act in many different tissues in different ways and under different stimulation. Interestingly, however, a specific peptide growth factor seems to be effective only on neuroectodermal or mesodermal or endodermally derived tissues.

Dr. Larry Shapiro reported that there is clearly a pseudoautosomal part of the short arms of both the X and Y chromosomes; this portion is shared and has obligatory crossover. Between the locus on the X chromosome and the centromere there is a steroid sulfatase (STS) locus. On the Y chromosome at the same site there is a pseudo-STS gene, and proximal to that on the Y chromosome is the testes-determining factor. Rarely in human beings is there crossover between the X and Y chromosomes below the pseudoautosomal area; this explains why there are occasional XX males and STS-deficient females.

A memorial symposium in honor of Dr. Joseph St. Geme was established, at which a review of cytomegalic inclusion disease was presented by Dr. Charles Alford. He pointed out that this disease, which leads to extensive teratogenic effects in human beings, is probably now the most serious preventable viral illness in pediatrics. Approximately 35,000 newborns in the United States are affected each year, and at least 20% have significant sequelae.

In his report, Dr. David Rimoin said that the Kniest syndrome, the spondyloepiphyseal dysplasias, and Stickler's syndrome all seem to have linkage to type II collagen. Dr. Hollister reported that Marfan's syndrome seems to be an abnormality of fibrilin. Monoclonal antibodies to fibrilin were used to identify Marfan's patients in a double-blind study. These patients have recognizable fibrilin abnormalities.

Dr. A. Fujimoto described a new autosomal dominant pseudocleft syndrome characterized by a broad nose, colobomas of the eye, and branchial arch involvement.

Dr. Claire Leonard reported several cases of craniosynostosis and facial dysmorphism associated with maternal hyperthyroidism. The thyrotoxic state appeared to trigger early fusion of the cranial sutures.

Dr. Colleen Morris discussed the findings of a survey of 81 patients with Williams' syndrome and defined an evolving natural history that changes from infancy to adulthood.

Dr. Judith Hall reported that gonadal mosaicism appears to be responsible for some autosomal dominant conditions—such as pseudoachondroplasia—seen in siblings with normal parents. As many as 3% of apparent new dominant mutations may actually occur because of gonadal mosaicism for the abnormal gene in one of the parents. That is, during embryologic development of the parent, a somatic mutation occurred, giving rise to some tissues that carry the mutation, but not enough tissues to express the disorder in the parent. However, the gonad or gonads would carry the mutation and therefore the condition can be passed on to more than one child in the family.

In Future Issues

The Concepts and Mechanisms of Genetic Linkage
by Thaddeus Kelly, M.D.

Restriction Fragment Length Polymorphism:
Applications to Linkage Analysis
by Thaddeus Kelly, M.D.

On July 1, 1987, Dr. James M. Tanner and Dr. William L. Clarke will join the Editorial Board of *Growth, Genetics, and Hormones*. Dr. Tanner, of the Institute of Child Health at the University of London, is noted for his work in anthropometrics. Dr. Clarke, of the University of Virginia Medical Center, Charlottesville, is a pediatrician and pediatric endocrinologist with a special interest in diabetes. Dr. Tanner and Dr. Clarke will be "introduced" more formally in the next issue.

Constitutional Delay of Growth and Adolescent Development

Jürgen R. Bierich, M.D.
Associate Editor
Growth, Genetics,
and Hormones

In 1957, Lawson Wilkins first gave a comprehensive description of a syndrome called "constitutional delay of growth and adolescent development (CDGAD)." His definition included retarded linear growth beginning early in childhood, retarded skeletal maturation (often with a two- to four-year delay), retarded sexual development, and a familial incidence. Wilkins stated, "A certain level of general maturity must be reached before the pituitary gonadotropic mechanism can be activated." In this way, the concept emerged that the delayed sexual maturity is a secondary phenomenon—a sequel to the retarded growth.

Numerous alternative names have been used to denote CDGAD. These include constitutional delay of development, idiopathic short stature, simple delay of growth, and essential growth retardation. CDGAD must be differentiated from "genetic short stature," which has been called "constitutional short stature" by some. Genetic short stature and CDGAD may occur coincidentally. Tanner et al coined the term "small/delay" for these patients. These patients have two common but distinct entities and not either simply CDGAD or simply genetic short stature. Furthermore, some of the children with "normal variant short stature" described by Rudman[1] have CDGAD; some children with what is today called "growth hormone neurosecretory dysfunction (GHNSD)" probably have CDGAD as well. Spiliotis et al[2] in 1984 wrote, "Children with GHNSD represent a substantial number of short children previously diagnosed as having CDGAD." Although one is justified in classifying children with short stature due to acquired cerebral lesions (particularly those lesions resulting from CNS irradiation) as patients with GHNSD, one would not be justified at this time to use this term to describe patients who may have CDGAD.

Incidence and Growth Patterns

CDGAD is more common than any other type of short stature. Estimates indicate that 60% to 90% of the parents of children with CDGAD themselves also experienced delayed growth and adolescent development. As a rule, this condition is inherited from one parent. Mendelian recessive inheritance, therefore, can be excluded. Simple dominant transmission is possible, but it certainly does not account for all cases.

The auxological features of CDGAD include normal birth length and weight. Growth velocity frequently slows during the first five years of life. When they begin primary school, these children are typically among the smallest. The growth curve then parallels the third percentile, and the velocity may sometimes be less than 3 cm/year.

The pubertal growth spurt commences two to four years after the usual age (mean age) for adolescent development, though this is the appropriate time based on skeletal maturation, and the peak height velocity is lower than average for children who mature at the usual time. Skeletal maturation is often delayed by several years. The high correlation coefficients between bone maturation and other parameters of development are presented in Table I.[3]

Endocrine Findings

The endocrinologic findings are related to alterations in gonadotropin, growth hormone (GH), and somatomedin-C (Sm-C) or insulin-like growth factor-I (IGF-I) secretion. The gonadotropin concentrations correlate with bone age and delayed maturation but not with the chronological age. In response to stimulation with luteinizing-hormone–releasing hormone (LHRH), the follicle-stimulating hormone (FSH) levels usually rise higher than do the luteinizing hormone (LH) levels. The reverse occurs as pubertal development ensues. It has been found that this test cannot differentiate patients with CDGAD from those with partial GH deficiency (GHD) that may be accompanied by a similar delay in skeletal maturation.

GH release following provocative stimuli (pharmacologic agents) is usually normal.[4-6] In a minority of children, the GH responses are within the hypopituitary range, but retesting these same children during puberty often yields peaks of GH concentrations that are within the normal range. For example, in 1979, Gourmelen et al[7] reported the results of ornithine stimulation of GH secretion in 105 children with retarded growth, the majority of whom had significant delay of bone age. Significant concentrations of GH were present after ornithine and/or insulin stimulation in 74, but not in 31. Of these, seven had confirmed GHD with peak lev-

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Table I. Correlation Between Bone Age (BA) and Parameters of Development (Coefficient of Correlation r) in Patients With CDGAD

Height age/BA	0.92
Testicular development/BA	0.86
Pubic hair/BA	0.83
17 oxosteroids/BA	0.71
Testosterone (urine)/BA	0.86

continued from page 9

els of less than 3 ng/ml. The remaining 24 children were between 11 and 15 years of age and in pubertal stages 1 and 2. Their peak GH levels were 3 to 8 ng/ml. Ten of these 24 were retested after reaching stage 3 of sexual development, and they had peak GH concentrations of between 8 and 45 ng/ml, with a mean of 21 ng/ml. The authors interpreted these observations as indicative of "transient-partial GHD." Other authors[5,8-10] have observed and reported similar instances in patients who appear to have GHD prepubertally but who have normal responses to provocative tests following the onset of puberty.

It is probably incorrect, however, to compare normal values obtained after the onset of puberty with the normal values found in prepubertal children. The mean stimulated values in normal adolescents are approximately twice those of prepubertal children. With stimulation, patients with CDGAD reportedly do not have GH peaks of the same magnitude as do normal children during puberty.

Because of the variability of results obtained after pharmacologic stimuli, several authors[5,11-13] have examined the spontaneous secretion of GH throughout the day or night or around the clock. In only a few instances were abormally low peaks found during sleep, eg, in two of 14 patients reported by Wise and colleagues.[13] In 1979, and again in 1985, Bierich and co-workers[14,15] investigated sleep-induced GH secretion. The results in children with CDGAD were compared with those in healthy controls with equivalent sexual maturation. These investigators determined the area under the GH-*v*-time curve to obtain the integrated total secretion over 5.5 hours at night. The highest peak levels were also determined. The results obtained from 124 patients and 28 controls are shown in Table II. These data indicate that patients with CDGAD secrete less GH at all stages of pubertal development than do control children. Differences between the patients and controls were statistically significant in all groups, except for those in stage 2 of sexual development. The interpretation of these data prompts the hypothesis that there is permanently diminished GH secretion.

A second form of growth delay, which is designated as "short stature due to an immunologically reactive but biologically inactive GH," is sometimes clinically indistinguishable from CDGAD. In this entity, growth retardation is presumed to result from the production of a GH molecule that is biologically inactive, since the GH levels are normal or high and IGF-I is low as in GH-deficient children. However, patients with this entity, which was described by Hayek and co-workers[16] and Kowarski et al,[17] are usually more severely retarded in growth than are patients with CDGAD. Subsequent patients also have been described by Bierich et al,[4] Rudman and coworkers,[1] and Valenta et al.[18] The only attempt to determine the structure of GH was made by Valenta et al,[18] who proposed a circulating GH molecule of abnormal structure. (See abstract in *Growth, Genetics, and Hormones*, Vol. 1, No. 4).

At least three groups of investigators have reported increased IGF-I levels in tall children (compared with children of normal stature); others have reported decreased IGF-I values in short children (compared with children of normal size).[19-21] Children with CDGAD have IGF-I values in accord with their skeletal maturation rather than with their chronological age. Link et al[22] demonstrated that the administration of testosterone to these patients increased both GH production and IGF-I levels. It is on this basis, as well as upon the observation that IGF-I levels increase early in puberty, that one may hypothesize that testosterone increases the circulating concentrations of GH and the generation of IGF-I in early adolescence.

Table II. Sleep-Induced GH Secretion in 124 Patients With CDGAD and 28 Controls

	Puberty stages					
	P_1		P_2		P_3	
(Number of cases)	(86)	(18)†	(31)	(3)†	(7)	(7)†
Sleep-induced GH secretion 5½ hrs (ng/ml × 330 min)	2469** ±1068	4349 ±1134	3347 ±1619	5905 —	3580** ±1633	9794 ±1711
Peak GH level (ng/ml)	22.5** ±12.1	38.8 ±14.0	27.2 ±16.6	49.8 —	21.2* ±8.1	66.2 ±27.0

**Statistically significant difference v controls P > 0.01*
***Statistically significant difference v controls P > 0.001*
†Control children

The Need for Therapy

The need for therapy and the treatment chosen should be considered for each individual child. The adult stature eventually reached by children with CDGAD varies considerably and is related to the heights of the parents. The majority of patients attain a height within the normal range, unless they are in the small/delay category. Nevertheless, Preece and colleagues[23] first demonstrated

that the adult height of those with CDGAD is below the mean for the general population. This was confirmed by Ranke et al.[24] Whether therapy will increase ultimate height or whether it will affect only the rate of growth during treatment is a question of great importance. If testosterone or androgens are used, one must consider whether adult height may be reduced. Treatment certainly is indicated in many patients and, in particular, in adolescent boys who are psychologically less able to cope with their shortness, their delayed sexual maturation, and their high-pitched voices. At no other time in childhood is the height gap with relation to age mates as great as it is during early adolescence, particularly since the growth rate of children with CDGAD reaches its nadir at the same time that the adolescent growth spurt occurs in normal children of the same age.

Treatment should be seriously considered for patients who are in danger of developing a severe inferiority complex. One of two forms of therapy can be chosen: the use of testosterone with or without anabolic steroids, or the use of GH.

Therapy With Testosterone and/or Anabolic Steroids

Testosterone and/or anabolic steroids have been employed for many years to treat CDGAD. The anabolic steroids are derived from testosterone. With the possible exception of oxandrolone (Anavar), all anabolic steroids display similar androgenic or virilizing effects—including increased skeletal maturation—in comparison with testosterone. However, oxandrolone has a significant growth-promoting effect in relation to its minimal, modest virilizing action. At a dosage of 0.1 mg/kg/day, oxandrolone has been used successfully in patients between the ages of 11 and 16 who are more concerned about their height than their delayed sexual development. In Europe, Stanhope and Brook[25] reported favorable results with oxandrolone in 24 boys with CDGAD.

The use of testosterone is limited to boys, usually 14 years of age and over, who have significant concern about their delayed sexual development. Martin and co-workers[26] showed that doses of 50 mg of a long-acting testosterone ester (testosterone enanthate) once a month will enhance sexual development without affecting adult height. Doses of 100 mg or greater very possibly reduce the ultimate stature. Treatment is often continued for six to 12 months, at which time the testosterone is discontinued to determine whether spontaneous puberty has occurred. Occasionally, a repeat course of therapy beginning six months after the end of the first course is appropriate.

Treatment with GH

Studies evaluating GH for the treatment of CDGAD are few in number. The first report of the successful administration of GH to such patients was from Grunt et al in 1972,[27] who stimulated growth in four of ten children with CDGAD. In a subsequent report by Kastrup et al,[8] growth velocity rose from 3.7 to 8.4 cm/year during therapy. Bierich and co-workers[4] in 1983 reported an increased growth rate (from 4.1 cm/year to 8.3 cm/year) with therapy. Gertner and co-workers[28] have reported similar findings. Individual differences are considerable, but the greater the delay in bone age, the better the acceleration of growth velocity. The growth rate in children with CDGAD had been maximal during the first year of treatment and decreased thereafter, a pattern that occurs with GH-deficient patients receiving GH.

Although adequate data are presently unavailable to evaluate the long-term effect of GH treatment on children with CDGAD, this author has the clinical impression that the growth prognosis of most of these children improves. Since none of the patients in our series has reached final height, no definitive statements can be made regarding an increase in ultimate height. At present, treatment with GH of patients with CDGAD should be reserved for the most severely dwarfed children. Additional studies under controlled conditions are urgently required before GH treatment—outside of centers where the efficacy of GH treatment in patients who are not GH-deficient is being studied—can be recommended for patients with CDGAD.

The use of other agents, such as growth-hormone–releasing hormone (GHRH) and clonidine, an alpha$_2$ adrenergic drug that stimulates the release of GH, requires further study. Results evaluating GHRH in the treatment of CDGAD have not been reported. In 1985, Pintor et al[29] administered clonidine to four patients with CDGAD over a period of two months, and they described increased values of circulating GH and IGF-I and accelerated growth. However, this is an exceedingly small series of patients treated for a short period of time. Currently, several investigators are involved in studying the effect of clonidine in CDGAD further.

Summary

CDGAD is the most common form of short stature. Preliminary studies suggest that children with CDGAD have inadequate GH production, whereas children of the same age who do not have CDGAD, have adequate GH production. Some would call this a physiological state (partial GHD). In this sense, CDGAD is similar to the previously described GHNSD. Testosterone, and probably estrogen as well, stimulates increased production and secretion of GH. This, in turn, stimulates increased IGF-I concentrations in normal early puberty.

The use of GH as a therapeutic agent in CDGAD is under clinical investigation. Currently, oxandrolone (0.1 mg/kg/day) is the treatment of choice in patients under 14 years of age who require a growth-promoting agent for primarily psychological reasons. Depotestosterone (long-acting enanthate or cypronate) is the

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treatment of choice for patients over 14 years of age who are concerned about delayed sexual maturation as well as short stature. GH, GHRH, clonidine, or all three may have therapeutic importance in the future for patients with CDGAD, but are not currently recommended except for patients enrolled in research protocols.

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Letter to the Editor
Another Perspective on Intrauterine Growth Retardation

Intrauterine growth retardation (IUGR) is a complex clinical condition that is directly related to maternal health and behavior during pregnancy and is in large measure preventable. The purposes of this communication are to illustrate the complexities in the epidemiology, pathogenesis, and diagnosis of IUGR, and to point out that the Denver fetal growth charts, which apparently are the most widely used in the United States,[1] are inadequate for diagnosing IUGR and consequently underestimate its frequency by a wide margin.[2,3]

Epidemiology and pathogenesis. It has been widely recommended that IUGR be diagnosed on the basis of a marked reduction in birth weight at a specific gestational age.[1,4] When IUGR is diagnosed by this method, any condition that lowers birth weight in relation to gestational age must be taken into account. There is an increasing awareness of a link between IUGR and low birth weight (LBW) to the extent that many growth-retarding conditions are common to both outcomes.[1,5,6] Most term infants with LBW have IUGR. The comprehensive report on the prevention of LBW[5] lists 41 principal risk factors associated with LBW; they include genetic, environmental, demographic, and socioeconomic conditions, medical and obstetric complications of pregnancy, fetal infections, and inadequate nutrition of fetuses. Most of these risk factors have been observed in term infants with IUGR.[7] With so numerous and so varied a list of risk conditions, it should not be surprising that some pregnancies are complicated by multiple risks that are associated with even greater reductions in birth weight that occur with single risks.[8] Single risks occur in some pregnancies, but they are less frequent than generally suspected (except for cigarette smoking, which has occurred in 30% to 40% of gravida in some populations).

There are three main types of IUGR; they differ in their pathogenesis, their frequencies, and in their postnatal courses. The symmetric type of IUGR is diagnosed by a short crown-heel length for gestational age. The asymmetric type, which is the least severe form of IUGR, is diagnosed by a low weight-height ratio or ponderal index. The combined type (symmetric and asymmetric) is the most severe type of IUGR and, fortunately, the least frequent. These infants are small for their dates and markedly deficient in soft-tissue mass.

These types can not be diagnosed from birth weight alone, but require measurements of crown-heel length and calculations of either weight-height ratios or ponderal indices. Accurate measurement of crown-heel length is not easy in infants who are tensed in the flexed position. Crown-heel lengths are more accurate when the infant is quiet and put in the tonic-neck reflex position that allows one leg to be straightened

more readily.

Diagnosis and frequency. The use of appropriately constructed fetal growth charts and tables for diagnosing IUGR at birth is critical in determining its frequency. Accurate determinations of weight and body measurements at birth are essential in every infant, not only to diagnose IUGR, but also to provide reliable baseline data for physicians evaluating postnatal growth of infants and children. Ultrasound methods for diagnosing IUGR prenatally have been improved, but the ultimate responsibility for diagnosing IUGR rests with the physician caring for the newborn infant.

The location of "bottom" lines on fetal growth charts used in diagnosing IUGR depends on the investigators who design them and who decide which infants are to be excluded from the charts and tables, how gestational age is to be determined, and whether the bottom lines should be located on the third, fifth, or tenth percentiles or at two standard deviations below the means. The extreme variations in the data and locations of bottom lines of fetal growth charts and tables in the United States have been described.[9] An example of these extreme variations is seen in the Denver charts and Kansas City tables of birth weights.[9] The bottom lines on the Denver charts (tenth percentiles) are 400g to 500g lower for infants than the bottom lines in the Kansas City tables (fifth percentiles). These differences produced a sixfold increase in the frequency of IUGR when the same group of infants was diagnosed using the Kansas City tables as compared with the Denver charts.[7] The explanation for the differences in bottom lines is partly related to Denver's mile-high altitude as compared with Kansas City's altitude (about 800 feet above sea level). But it is also related to a marked difference in the criteria for excluding infants from the charts and tables. Infants were excluded from the Kansas City tables if their mothers had any of a long list of risk conditions.[7] Infants were excluded from the Denver charts if their mothers had diabetes or if hydrops fetalis or major congenital malformations were present. These exclusions amount to a small percentage of the many risk conditions that have the potential for retarding fetal growth. Untold numbers of infants born to mothers with potential fetal-growth-retarding conditions that were present during their pregnancies were included in the Denver charts.

The diagnosis of IUGR is further complicated by conditions present in all pregnancies that have the potential for lowering birth weight significantly. These are maternal race, height, weight-height ratio at conception, parity, and age, and sex and gestational age of infants.[10,11] These conditions require that either special fetal growth tables be constructed for each condition or that these universally occurring conditions be controlled when diagnosing infants with IUGR. For example, reported data indicate that black infants born at term to low-risk mothers delivered at the University of Kansas Medical Center are smaller and weigh less at birth than white infants of the same gestational age and sex when controlling for mother's socioeconomic status, risk conditions, height, weight-height ratio at conception, gravidity, parity, and weight gain during pregnancy.[12] Another study suggests that black infants born to mothers who smoke heavily (>10 cigarettes per day throughout pregnancy) have lower birth weights than infants of white mothers born under similar circumstances.[13] Cigarette smoking during pregnancy is almost certainly one of the most, if not *the* most, frequent risk condition associated with IUGR. The Denver charts do not take cigarette smoking into account and do not provide data on fetal growth of blacks.

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Dr. Blizzard's comments

Dr. Joseph Warshaw's article in *Growth, Genetics, and Hormones* ("Perspectives of on Intrauterine Growth Retardation," Vol. 2, No. 4) prompted Dr. Herbert Miller to respond with his perspective on IUGR. These two presentations complement each other exceedingly well. All readers who are interested in this important topic will benefit from comparing these perspectives.

Insulin-like Growth Factors I and II: Evaluation of Growth Retardation

Rosenfeld et al measured plasma insulin-like growth factor (IGF-I and IGF-II) levels in 197 normal-sized children, in 44 normal short-statured children (NL-SS) with normal growth hormone (GH) release in response to pharmacologic stimuli, and in 68 GH-deficient children. Because of the variation in IGF-I levels related to age and sex, the results were stratified by sex into six age groups. Normal percentile curves were constructed for each group. The results for all groups are shown in Table I.

Evaluation of the mean IGF levels according to patient status and age groups provided the following analysis. Mean IGF-I levels in GH-deficient children were significantly below the mean levels seen in children of normal stature in each of the six age groups. IGF-II levels were significantly below the mean levels in only 50% of the group with GH deficiency (GHD). There were significant differences between the mean levels of IGF-I and IGF-II in normal and NL-SS children who were younger than 8 years of age, but these differences were not consistent by gender.

Analysis of both assays according to patient status is shown in Table II. When IGF-I and IGF-II levels were used in combination, the distinction between normal and GH-deficient children was more pronounced than when either assay was used alone. Only one (0.5%) normal child and five (11%) short normal children had low plasma levels of both IGF-I and IGF-II. On the other hand, only three (4%) GH-deficient children had normal plasma levels of both somatomedins.

Rosenfeld RC et al. *J Pediatr* 1986; 109:428.

Table I. Percentile Curves

	IGF-I		IGF-II	
	5-95th*	< 5th*	5-95th*	< 5th*
Normal (197)	98%	2%	95%	5%
GHD (68)	18%	82%	58%	52%
NL-SS (44)	68%	32%	65%	35%

**Percentiles*

Table II. Analysis of IGF-I and IGF-II assays

	NL/NL*	NL/L†	L/L‡
Normal (197)	93%	6%	1%
GHD (68)	4%	59%	37%
NL-SS (44)	46%	43%	11%

** Both IGF-I and IGF-II levels are between the 5th and 95th percentiles.*
† Either the IGF-I or the IGF-II level is between the 5th and 95th percentiles.
‡ Both IGF-I and IGF-II levels are below the 5th percentile.

Editor's comment—*The data from this large series of children may serve as a first order attempt at differentiating short normal (but GH-sufficient) children from those with GHD. If only it were so simple! First, IGF-II determinations are not routinely available. Although the children in each of the two short-stature groups were separated by responses to pharmacologic provocative tests for GH secretion, the categorization of children into GH-sufficient and GH-deficient groups is accurate only at the extremes. There are a number of children with a GH-deficient phenotype who respond to pharmacologic stimuli by releasing GH, but who do not grow well. Are they physiologically deficient in GH?*

How one answers depends upon the "definitions" used. In fact, it is not so important to label or categorize each patient by GH response to stimuli, but to determine prospectively which children are likely to respond to exogenous hormonal therapy—be it recombinant human growth hormone (hGH) or (in the future) recombinant IGF-I. Thus, many short children may have a neurosecretory alteration that does not permit enough GH to be secreted at the proper intervals to maintain liver and tissue growth factor levels, thereby preventing the child from reaching his or her genetically determined growth potential.

The unavoidable implication of GH secretory pattern studies, especially when combined with the observations in this report, is that the diagnosis of GHD based on the results of provocative tests is both arbitrary and nonphysiologic. Suboptimal GH secretion or activity may be reflected in decreased GH pulsatility, reduced integrated GH concentrations, or suboptimal IGF-I and/or IGF-II levels. With the imminent availability of essentially unlimited quantities of hGH (and IGF-I), the ability to determine which short children are most likely to have accelerated growth (catch-up growth) in response to therapy with these growth factors becomes of paramount importance.

Alan D. Rogol, M.D., Ph.D.

Growth, Bone Maturation, and Biochemical Changes in Brazilian Children From Two Different Socioeconomic Groups

Growth and bone maturation were measured to assess the influence of malnutrition on growth in two groups of children and adolescents (ages 7 to 17 years) in Brazil. The groups (674 from the upper socioeconomic class and 226 from the lower socioeconomic class) were evaluated for weight, height, and bone age. Biochemical measurements, including plasma calcium, phosphorus, alkaline phosphatase, and serum proteins, were also taken.

The growth of children from the upper socioeconomic class was similar to American standards for growth, with the mean weight and height following the 50th percentile curves on the National Center for Health Statistics growth charts. However, the children from the lower socioeconomic class were underweight for their height and growth retarded for their chronological age. Their mean values for weight and height fell below the 25th percentile on the same growth charts. Interestingly, boys were more severely affected, with many having height measurements below the 5th percentile.

Evidence of delayed skeletal maturation was seen in only 9% of the upper socioeconomic class children, while 84% of the lower socioeconomic class children had a delay in bone age of at least two years. Boys were more affected than girls, and bone age delays of greater than three years were seen only in boys. Abnormal bone structure, including evidence of growth arrest and fewer coarse trabeculae, was also found in 13% of the children in the lower socioeconomic class.

Plasma calcium, magnesium, vitamin D, and total protein levels were similar in both groups of children and no signs of rickets were found. In underprivileged children, albumin levels were significantly lower ($P < 0.001$) and plasma alkaline phosphatase and phosphorus levels remained elevated even after the predicted age of the adolescent growth spurt had been reached. Menarche was delayed by two years in the girls of the lower socioeconomic class.

Linhares EDR et al. *Am J Clin Nutr* 1986;44:552.

Editor's comment—*The authors describe a serious problem of chronic malnutrition in the lower socioeconomic class that affects as many as 50% of Brazilian children. This study also points out that environmental conditions may be more important than racial factors in influencing growth. Privileged Brazilian children grew and developed as well as American children.*

The gender differences in height and development may also be culturally induced. The more severely impaired growth seen in underprivileged boys may reflect the fact that adolescent boys are forced to find work while the girls remain at home. Long hours and poor working conditions generally affect health and nutritional status adversely, thus resulting in impaired growth and delayed adolescent development. Effective programs to protect the young in underprivileged communities, where malnutrition is prevalent, could alleviate the unfortunate consequences of nutritional dwarfing.

Fima Lifshitz, M.D.

Growth in Thyrotoxicosis

Buckler and co-workers followed 46 children and adolescents who developed thyrotoxicosis after infancy to determine the effects of this condition on growth velocity, adolescent development, and ultimate height. As expected, girls with thyrotoxicosis outnumbered boys in this study, where 41 of the 46 subjects were female. Diagnosis was based on symptoms, clinical signs, and biochemical measurements of thyroid hormone levels. All but two subjects were adequately controlled by medical treatment, as determined by clinical and biochemical criteria.

At presentation, most of the children had heights above average and some were very tall (average, + 0.75 SD). The skeletal age was often more advanced than the height age, but to a variable degree. The children were underweight for age (average, − 0.32 SD) and thus quite underweight for height.

Ultimate height for the girls was + 0.54 SD, which is greater than their target height (+ 0.0 SD) based on the midparental centile values.

Buckler JMH et al. *Arch Dis Child* 1986;61:464.

Editor's comment—*As expected, these children were tall and had advanced bone ages at presentation. The advanced bone ages were often out of proportion to the increase in height. However, the ultimate height prognosis was good, which is not the case with patients whose increased height and advanced bone age are accompanied by virilizing adrenal hyperplasia or precocious puberty. What cannot be determined is the role of "good control" of thyrotoxicosis on ultimate height, since many patients had periods of mild toxicity or mild hypothyroidism while on therapy.*

Alan D. Rogol, M.D., Ph.D.

MEETING CALENDAR

June 14-18 27th Annual Meeting of the Teratology Society. Marriott Rancho Las Palmas Resort, Rancho Mirage, California. Contact: Alexandra Ventura, Teratology Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1841)

July 19-22 Clinical Genetics Conference: Neural Crest and Craniofacial Disorders. March of Dimes–Birth Defects Foundation and the University of Minnesota, Twin Cities. Radisson Hotel, Minneapolis, Minnesota. Contact: Dr. Robert Gorlin, University of Minnesota School of Dentistry, 515 Delaware Street SE, Minneapolis, MN 55455

August 15-19 David Smith Malformations and Morphogenesis Meeting. Furman University, Greenville, South Carolina. Contact: Dr. Roger Stevenson, Greenwood Genetics Center, 1 Gregor Mendel Circle, Greenwood, SC 29646 (803-223-9411)

September 6-11 9th International Workshop on Human Gene Mapping. Paris, France. Contact: Prof. Jean Frezal, Hôpital des Enfants Malades, 149 Rue de Sevres, 75743 Paris CÉDEX 15 France. (1-42 73 80 00)

September 11-12 New Genetics and the Human Gene Map. Paris, France. Contact: Prof. Jean Frezal, address and phone as above.

September 28-30 International Congress on Advances in Growth Hormones and Growth Factors Research. Milan, Italy. Contact: Drs. Daniela Cocchi and Vittorio Locatelli, Department of Pharmacology, Chemotherapy, and Toxicology, University of Milan, Via Vanvitelli 32, 20129 Milan, Italy

October 7-10 38th Annual Meeting of the American Society of Human Genetics. Town and Country Hotel, San Diego, California. Contact: Administrative Office, American Society of Human Genetics, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1825)

Growth, Genetics, and Hormones is published under an educational grant from Genentech, Inc.

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New York, NY 10164-0569

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GROWTH
Genetics & Hormones

Vol. 3 No. 3 September 1987

Genetic Linkage: Introduction to Basic Concepts

Thaddeus E. Kelly, M.D., Ph.D.
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Charlottesville, Virginia

Analysis of the linkage of genes and the construction of gene maps are basic approaches to understanding how genes control both normal and abnormal physical and biochemical differentiation and function of the human organism. During the past 10 years, the development of recombinant DNA technology and its utilization in mapping genes have greatly enhanced our knowledge in these areas and, concomitantly, have increased the application of this information to clinical medicine. This article is presented to clarify concepts about genetic linkage and to sharpen the reader's understanding of gene linkage and its implications.

Practical Applications of Gene Linkage and Mapping

If a genetic disorder segregates in families and is consistent with a mutation at a single gene locus, the location of that gene within the entire human genome can potentially be mapped. This can have several practical applications:

1. To determine whether a molecular defect in a clinical condition, such as genetic growth hormone (GH) deficiency, is due to an absence or to a mutation of a specific gene.
2. To determine if clinical conditions with similar characteristics

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In This Issue

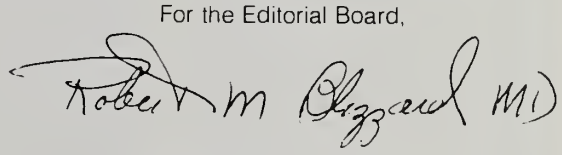
Letter From the Editor

Dear Colleague:
An understanding of the genetic approach to diagnosis and treatment is essential for all pediatricians, regardless of subspecialty. The complexities of this approach are great; indeed, comprehending the language and the tools of the geneticist is a challenge for many of us.

Since a major goal of this publication is to expose our readers to a concise review of important current topics, we invited Dr. Thaddeus Kelly to write two articles to introduce us to the geneticist's current approach to the diagnosis and treatment of inherited diseases. In my letter to you in *Growth, Genetics, and Hormones*, Volume 3, Number 1, I stated, "We encourage you to set aside a few hours for studious review of Dr. Kelly's articles; they will be well worth your time and professional interest." I am now encouraging you to follow my suggestion to curl up in a chair away from the phone and to read and study Dr. Kelly's two contributions published in this issue. The investment of time will be rewarding, and the articles will provide you with a basis for understanding more detailed information regarding our capability to pursue the diagnosis and treatment of inherited diseases.

As an interested reader, you can expand your knowledge by reading an excellent article on this topic published in the *Mayo Clinic Proc* (1987;62:387-404) by Dr. S.S. Sommer and Ms. J.L. Sobell. The title of the review is "Application of DNA-based Diagnosis to Patient Care."

For the Editorial Board,



Robert M. Blizzard, M.D.
Chairman

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occurring among members of unrelated families are actually identical in origin. This can be done by studying the genes of affected individuals for identity or non-identity. For example, patients with types IA and IB of genetically inherited GH deficiency have non-identity, or different etiologies. In type IA, the GH gene is missing. The gene is present in type IB.

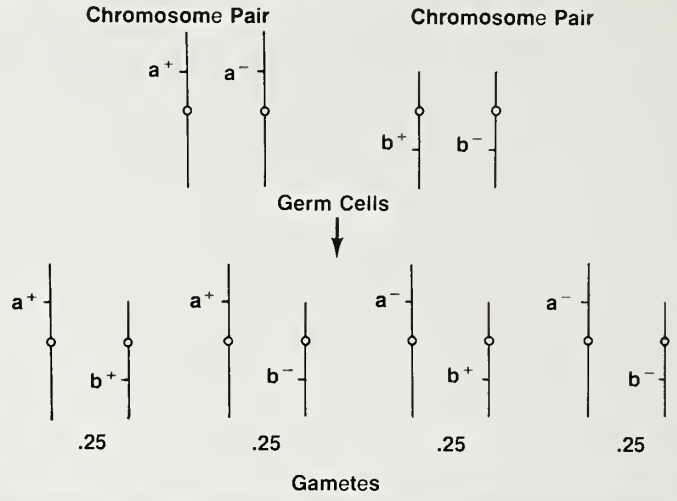
3. To diagnose certain clinical conditions by determining gene haplotypes (eg, HLA types), since there is genetic linkage between certain conditions and the HLA loci. Congenital virilizing adrenal hyperplasia can be diagnosed in a fetus by studying the HLA haplotypes of the fetus, its parents, and its affected sibling.
4. To design replacement therapy for a missing gene product, such as GH, by utilizing recombinant DNA techniques.
5. To design methods for the insertion of normal genes into an affected fetus or child. A possible application could be in the Lesch-Nyhan syndrome.

Gene Alleles, Meiotic Segregation, and Gene Crossover

When the genes for a trait are identical in all individuals, the genes are said to be *monoallelic*. When multiple variations occur in gene structure, *polyallelism* is said to be present whether gene function is normal or abnormal. For example, the presence of various alleles for the HLA-A locus (HLA-A1, A2, etc) is termed polyallelism. Similarly, polyallelism also occurs when the variations lead to abnormal gene function.

During the first cell division of meiosis (the reduction division from 46 to 23 chromosomes), the members of each pair of homologous chromosomes separate and each daughter cell ends up with one or the other chromosome of a pair. *Segregation* of alleles at a given gene locus occurs during this stage of meiosis. Alleles at loci on non-homologous chromosomes will *assort* randomly, as illustrated in Figure 1. The alleles a^+ and a^-, one on each chromosome of a homologous pair of chromosomes, and the alleles b^+ and b^-, also one on each chromosome of another homologous pair, assort randomly in meiosis. With respect to these two gene loci, four types of gametes are produced with equal probability.

Figure 1. The alleles at two loci on different chromosomes (a^+, a on one chromosome and b^+, b on the other) assort randomly in meiosis. Four types of gametes are produced with equal probability.



Logically, all the genes present on a single chromosome should be transmitted intact as a unit during meiosis. However, a phenomenon of gene transfer called *crossing over* often occurs between the chromosomes of each chromosome pair during the first cell division of meiosis, as diagrammed in Figure 2. Crossovers result in new combinations of maternally-derived and paternally-derived alleles in the chromosomes of gametes. Although only one crossover or recombination is diagrammed in Figure 2, a pair of large chromosomes may have three or four crossovers per meiotic cell division.

The result of crossing over is that the alleles initially at two loci on the same chromosome may or may not assort randomly during meiosis. The frequency of crossing over between two loci depends primarily on the physical distance between the two loci. As shown in Figure 3, when the two loci of interest (A and B) are on opposite arms of the chromosomes, crossing over between these loci takes place readily and frequently during meiosis. If, however, the two loci of interest (B and C) are closely associated on the chromosome, crossing over between these loci occurs rarely. This results in *non-random assortment*, which occurs only when the loci are *linked* or very close together.

Address for Correspondence

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Figure 2. Crossing over between a pair of homologous chromosomes in meiosis results in a new combination of maternally and paternally derived genes in the recombinant chromosomes. The figure shows one crossover; a pair of large chromosomes will typically have three to four crossovers per meiotic cell division.

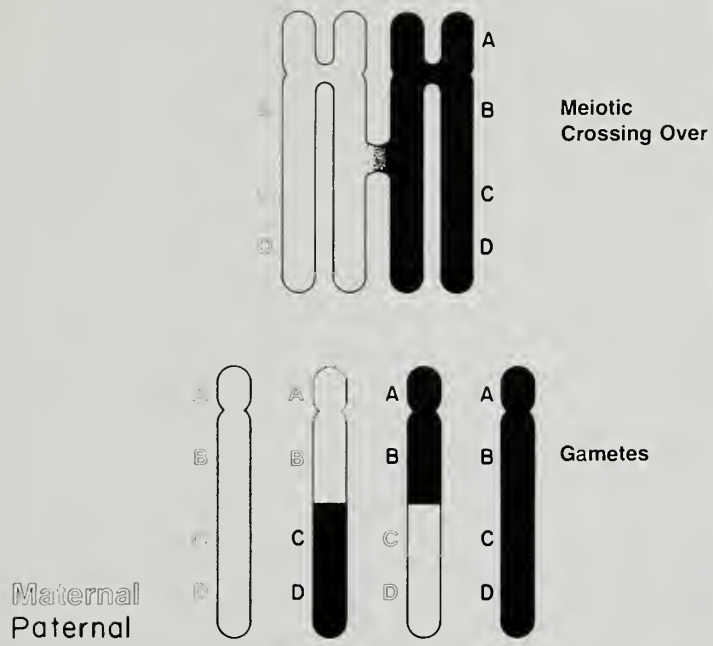
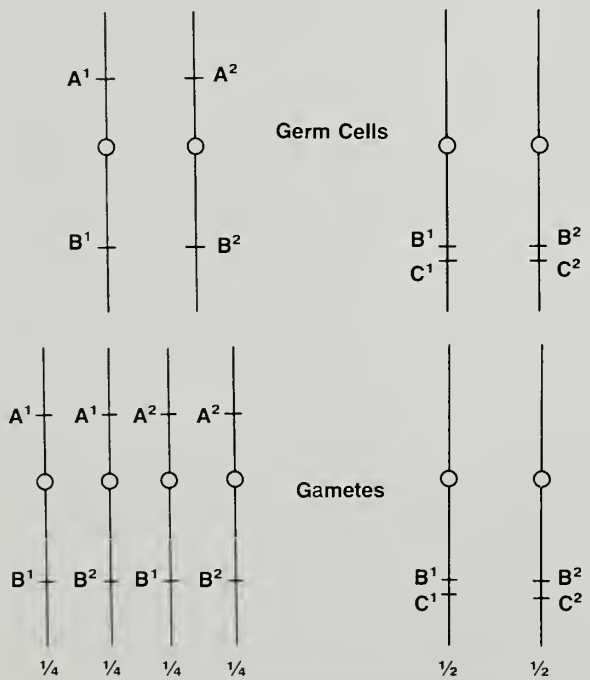


Figure 3. The alleles at two loci (A and B) on the same chromosome may be sufficiently far apart that assortment is random, or the loci (B and C) may be sufficiently close that they segregate as a unit.



Determination of Informative and Non-Informative Matings

A person may have two homologous (paired) chromosomes but be heterozygous for the alleles at each of two loci (for example, A1 and A2 at locus A, and B1 and B2 at locus B, as diagrammed in Figure 4). When geneticists speak of *alleles of interest*, they usually mean the mutant or the less frequent alleles that are used to study linkage. When both *alleles of interest* are on the same chromosome, as are A2 and B2 in individual X in Figure 4, the alleles of interest are said to be *in coupling*. If the two alleles of interest are on opposite homologous chromosomes, as are A2 and B2 in individual Y in Figure 4, the alleles of interest are said to be *in repulsion*. The state of these relationships is referred to as *the coupling phase or state*. Crossing over between the two loci results in a reversal of the coupling phase and is called *recombination*.

Families in which a member has a specific disease (the individual is referred to as the *proband*) can be studied for possible linkage of genes. The study of linkage in a sibship requires that the parents of the siblings be *informative* for linkage analysis. An *informative mating* is one in which the genotypes of the parent will allow for the recognition of genetic recombination or non-recombination in their offspring. The determination of linkage between two loci is based on an analysis of the frequency of recombination among the alleles of interest in the proband and his or her siblings.

A classic example to eludicate whether a *mating is informative* is in the study of the relationship of the gene locus of the ABO blood-type and the locus of a "structural gene" which, when mutated, results in the nail-patella syndrome. To analyze linkage between these two loci, it is essential that the affected individual be heterozygous at both the ABO locus and the locus for the nail-patella syndrome. The ideal mating for linkage analysis exists if the affected individual has type AB blood and is married to an unaffected indi-

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vidual with type O blood. If the affected individual has type O blood and the mate also has type O, it is not possible to determine if recombination occurs between the two loci since homozygosity for type O is present at the blood type loci of both mates; this precludes studying linkage and is referred to as a *non-informative mating*.

If no linkage exists between two loci, assortment of the genes at these loci is random, and recombination should occur 50% of the time. There is equal likelihood that an offspring will receive either an apparently unchanged parental haplotype or one in which the coupling phase is reversed. On the other hand, if the two loci are physically linked, analysis of the genes of the offspring will show distortion of this segregation ratio with a *recombination frequency of less than 50%, which is "linkage" by definition*.

Restated, a double heterozygote for two *unlinked loci* will produce four types of gametes with equal frequency (25% each). This is shown in Figure 3. The distortion by linkage of the expected 25%:25%:25%:25% segregation of two loci is dependent on the frequency of crossing over between the two loci. With *linkage of two loci* and a *recombination frequency* of 20%, the *segregation ratio* of the gametes becomes 40%:40%:10%:10%, as diagrammed in Figure 5.

Studies of Linkage Analyses by Traditional Studies of Families

For years, the analysis of linkage of gene loci was restricted to the construction of pedigrees in which a single gene-determined disorder was segregating and in which the analysis of a limited number of genetic markers might indicate linkage. The available genetic markers included red blood cell antigens, such as ABO, Kell, Rh, Duffy, and polymorphic plasma proteins, such as the amylases, haptoglobins, and peptidases.

Figure 4. The coupling phase of linked loci refers to whether the "alleles of interest" are on the same chromosome ("cis" configuration) or on opposite chromosomes ("trans" configuration).

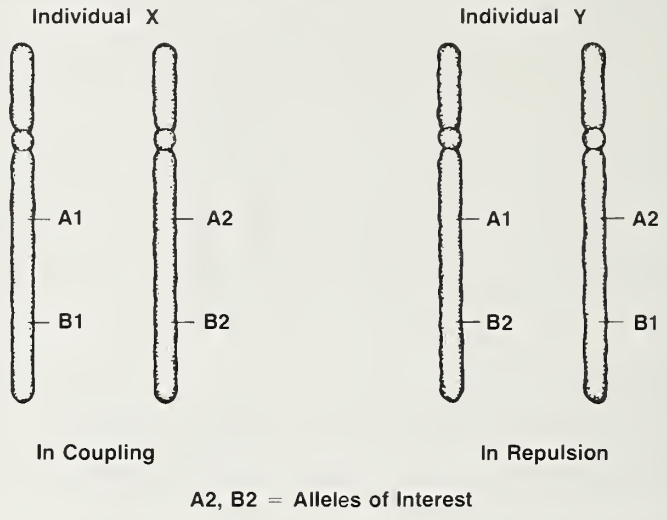
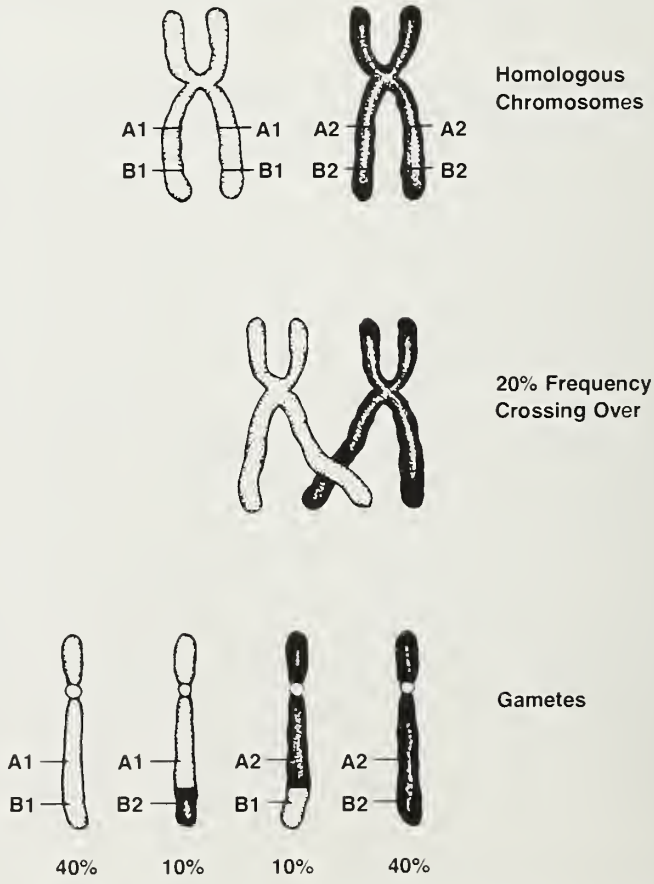


Figure 5. The distortion of the expected 25%:25%:25%:25% segregation of two loci by linkage is dependent on the frequency of crossing over between the two loci.



The investigator had no prior knowledge of the likely chromosomal assignment of the gene under study and, often, many of the families studied were not informative for linkage analysis, because of a low order of polymorphism for many genetic markers. Furthermore, the available markers for linkage analysis covered only a small portion of the human genome.

Nevertheless, this proved contributory and clinically helpful in certain studies. Dupont et al used this traditional approach in 1977 to establish linkage between the HLA locus and the structural locus for the steroidal 21-hydroxylase enzyme. This important finding provided a method to identify fetuses affected with congenital virilizing adrenal hyperplasia (CVAH). A pedigree reported by Dupont et al is diagrammed in Figure 6; a, b, c, and d represent specific HLA haplotypes. In the father, the HLA haplotype A24, B35, C4 (designated b) is in coupling with the mutant allele for 21-hydroxylase; in the mother, the mutant allele for 21-hydroxylase is in coupling with A1, B8 (designated d). Two of the children were affected. Note that the unaffected child, having received the mutant allele from the father and the normal allele from the mother, is a carrier for 21-hydroxylase deficiency. Determination of HLA typing permits the physician to determine if any unaffected person in the family is a carrier for the mutant gene and whether the mutant gene in an unaffected person is derived from the mother or father.

The Significance of the LOD Score

The *LOD score* or *logarithm of the odds* is a mathematical statement of the probability of linkage between two loci at a specified rate of recombination. The distance between two linked loci is expressed as a function of the frequency of recombination.

Establishment of linkage is determined by generating a LOD score. The probability that the observed segregation of alleles within families represents linkage can be compared with the probability that these same observations would occur if no linkage exists between the two loci under consideration. When the coupling phase in the heterozygous mate can be determined, as with codominantly expressed traits such as HLA, and if heterozygous children can be separated from homozygous normal children, the number of recombinants and nonrecombinants can be directly counted among the offspring.

The LOD score is calculated by means of a complex formula to determine if two loci are linked and, if they are linked, to determine the best estimate of the distance between the loci. In the LOD score equation, various estimates of the frequency of recombination (theta) are used to determine the frequency of recombination that gives the highest LOD score. The value for theta that gives the highest LOD score is taken as the best estimate of the frequency of recombination between the two loci under study. A LOD score of 3 or greater establishes linkages. A LOD score of 3 (for a given value of theta) means that it is 1,000 times more likely that the observed pattern of non-recombinants and recombinants occurred because of linkage rather than because of chance. (The LOD score equation, along with an explanation for its usage, will be provided to readers upon request.)

Limitations in the Use of Linkage for Diagnosis

There are some limitations in the use of genetic linkage for diagnosis, as mentioned previously when discussing the linkage of the ABO blood group and the nail-patella syndrome. In this instance, the affected individual would have to be heterozygous at both gene loci. To say that linkage analysis is possible for 85% of at-risk couples implies that the frequency of polymorphism at the linked genetic marker renders 85% of couples informative and 15% noninformative for analysis.

The second limitation is related to the distance between linked loci. The greater the distance between linked genes, the greater the likelihood that recombination would separate the linked genes and lead to error in the calculations.

Neither of these limitations is signficant for the prenatal diagnosis of CVAH by HLA typing. The high rate of polymorphism of

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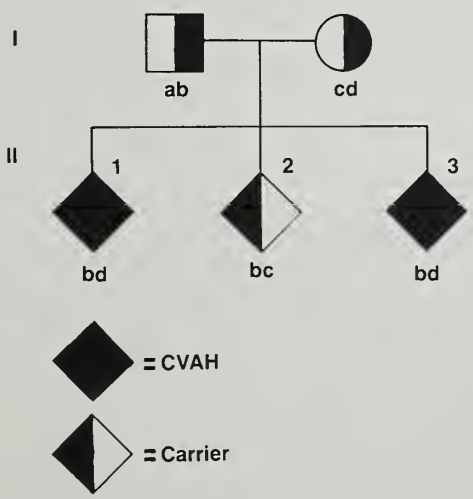
Figure 6. The two children with CVAH in this family were concordant at the HLA loci, while the second-born child is a carrier of 21-hydroxylase deficiency (from Dupont et al).



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alleles at the HLA loci renders most at-risk couples informative. Moreover, the distance between the HLA-B and 21-hydroxylase loci is so minute that no recombination with separation of these two alleles has been observed. Therefore, the potential error is minuscule.

Summary and Comment

Currently, a major research goal in human genetics is to develop genetic markers that are regularly spaced throughout the human genome at a maximum distance of 30 to 40 cM (centiMorgans). Such a set of markers currently exists for the human X chromosome. When identified for other chromosomes, it will be possible to map the unique structural genes within the human genome. Precise mapping of a locus will be the first step in determining the molecular basis for many disorders (such as Huntington disease and cystic fibrosis) and is essential for treatment based on genetic engineering. The advent of recombinant DNA techniques and their utilization in gene mapping and linkage analysis have led to great progress toward these goals. These techniques are discussed in greater detail in the accompanying article.

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Restriction Fragment Length Polymorphism: Applications to Linkage Analysis

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Restriction endonucleases are enzymes that cut DNA at specific nucleotide sequences (called "recognition sites") that are composed of 4 to 6 nucleotides. For a restriction endonuclease to cut both strands of double-stranded DNA, the sites must be mirror images or *palindromes* of each other. For example, the palindrome recognized by Eco R1 is GAATTC on one DNA strand and CTTAAG on the other. If this sequence is altered, the enzyme will not cut the DNA at that location. These naturally occurring differences, which are called *polymorphisms* in nucleotide sequence, at restriction endonuclease recognition sites result in the generation of DNA fragments of different lengths; these are referred to as restriction fragment length polymorphisms, or RFLPs. Because the restriction sites (and their variants) are inherited in families as Mendelian traits, RFLPs can be used for linkage analysis in the same manner as other biochemical or genetic markers.

RFLP analysis can be combined with other methods of gene mapping to allow study of diseases not previously approachable at the molecular level. RFLP analysis is made possible by the availability of a large number of DNA probes and restriction endonucleases, which will be discussed in greater detail. This will be followed by a discussion of the study of genetic heterogeneity by RFLP analysis and how diagnosis by RFLP analysis is accomplished.

In molecular genetics, a probe is defined as a DNA or RNA sequence that has been tagged with a radioactive element and is used to detect the presence of a complementary sequence by molecular hybridization. DNA probes for RFLP analysis are of three types.

1. Complementary or copy DNA (cDNA) probes are manufactured using the messenger RNA (mRNA) for a specific protein as a template. These probes contain the coding DNA sequence of only the exons of the structural gene; the introns have been excised during the processing to form mature RNA.

2. Genomic DNA (gDNA) probes are generated by first digesting genomic DNA with a restriction nuclease, followed by random insertion of the DNA fragments into a vector. A vector is a plasmid or phage used to carry a DNA segment that is to be cloned. *E coli* are then infected with the vector, and many copies of the DNA segment are produced. These segments can be separated from the vector and purified. This approach generates a library of DNA fragments and many of these prove to be useful as probes. The gDNA sequences that are useful as probes are those that contain unique DNA sequences that match (are complementary to) a specific location in the human genome. These probes contain both exons and introns.

3. Synthetic oligonucleotide probes are complementary to segments of structural genes and are manufactured using the amino acid sequence that forms a portion

of the protein molecule from which one can then deduce the nucleic acid sequence of the structural gene. Only 16 to 18 nucleotides of the proper sequence are necessary to generate a complementary probe. A complementary probe requires the specific nucleotide sequence of the structural gene.

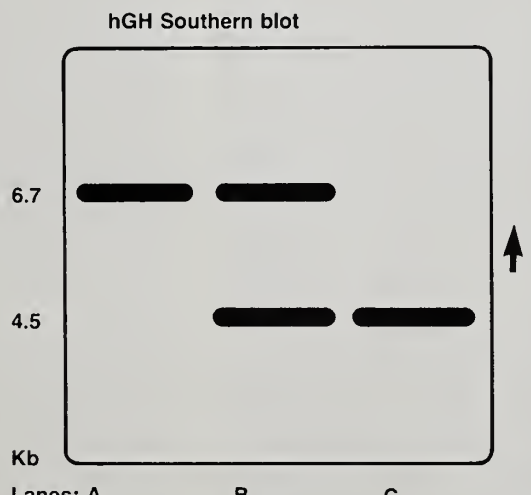
The concept of linkage analysis with RFLP is illustrated in Figure 1. A Southern blot study is used to evaluate polymorphism or polyallelism for the growth hormone (GH) gene. An endonuclease called Hinc il was used to generate fragments from chromosome 17 where the GH gene is located. A cDNA probe generated from mRNA for hGH is used to study the length (polymorphism) of the gene fragments. Polymorphism occurs normally for the GH gene, as studied by Hinc II endonuclease. The fragments of one allele are 6.7 Kb in length and the other, 4.5 Kb. Individuals may be homozygous for the 6.7 Kb fragment (46% of the population), homozygous for the 4.5 Kb fragment (10% of the population), or heterozygous with each allele present (44% of the population). Linkage analysis or use of linkage for diagnosis requires that the individual be heterozygous. To increase the capability for linkage study, other restriction enzymes can be used to break the GH gene into different fragments and further heterozygosity can be demonstrated. Two enzymes, Msp I and Bgl II, along with Hinc II, have been particularly useful in rendering most matings informative for linkage analysis with hGH probes.

RFLP analysis of the GH gene has permitted the identification of one type of inherited isolated GH deficiency, IGHD-IA, where the affected individuals are homozygous for absence of the gene. In some instances, the affected individuals have been found to have a deletion of only part of the GH gene. Studies using RFLP analysis in other families with inherited GH deficiency have not identified either absence of the GH gene or concordance for the genotypes of the hGH gene among affected siblings. Consequently, a cause for the GH deficiency other than an abnormality of the GH gene must account for the problem. These patients are currently said to have IGHD-Type IB.

Maury et al carried out similar studies of children having the GH deficient-like phenotype attributed to immunoactive, biologically-inactive GH. The low concordance rate for RFLP suggested that most children with this phenotype are not homozygous for a mutation of hGH structural genes.

These studies demonstrate that hGH genotyping with an hGH DNA probe and RFLP analysis can separate individuals who are affected with what appears to be the same disease from each other with respect to etiology. Carriers of a trait can also be identified by these techniques.

Figure 1. Autoradiography of fragments resulting from Hinc II endonuclease digest of hGH genes from 3 normal individuals is shown. Lane A has fragments from a homozygote for the 6.7 Kb band only, lane C has fragments from a homozygote for the 4.5 band only, and lane B has fragments from a heterozygote for the 4.5 and 6.7 bands.



Application of RFLP Linkage Analysis to Single Gene Disorders

Diagnoses utilizing RFLP linkage analysis can be extended further by comparing genotypes between a known affected member of a family and a member whose status is unknown. The approach is applicable to single gene disorders inherited as autosomal dominant, autosomal recessive, or X-linked traits. Currently there are four instances in which such an approach is useful.

The first occurs when there is clinical ambiguity or indecision as to whether a particular member of a family has the same disease as an affected member of the family. Disorders inherited as autosomal dominant traits, such as Marfan syndrome, often display variable phenotypes that may render the clinical diagnosis difficult in certain members of the family. Genotype analysis by RFLP studies may offer assistance in this situation. However, such analysis is not helpful in the diagnosis of an isolated case, except in rare instances where a gene deletion might be detected.

The second occurs when predictive testing is important to evaluate whether a member of a family with a disorder that makes its appearance late in life, such as Huntington disease, will develop that disease. The issue is important for genetic counseling and life-style planning. Non–insulin dependent diabetes mellitus and autosomal recessive primary hemochromatosis are similar examples. The latter may be diagnosed by link-

continued on page 8

Restriction Fragment Length Polymorphism

continued from page 7

age analysis using HLA typing and DNA analysis.

The third occurs when detection of carriers is important. This is particularly pertinent for X-linked diseases, since testing by methods other than RFLP analysis has been fraught with many ambiguities because of the peculiar biology of X-linked expression in heterozygous females. RFLP analysis is increasingly providing less ambiguous methods of carrier detection and is applicable currently to detect carriers for Duchenne muscular dystrophy or hemophilia A or B.

The fourth is for prenatal diagnosis of various congenital anomalies or diseases. This permits the option of terminating the pregnancy (if the fetus has an untreatable severe disease) or the development of fetal therapy in other conditions such as congenital adrenal hyperplasia.

The progress made in recent years in mapping the human genome has created significant advancement in both diagnosis and therapy of inherited defects and a new era of multidisciplinary research with achievable goals. An immediate goal of this collaborative effort is the construction of a gene map for each chromosome that is adequate to permit linkage analysis and, thus, mapping of any gene locus. The mapping of a gene locus is no longer considered an esoteric exercise, but a crucial step in understanding disease mechanisms. Now that the genes for Huntington disease, cystic fibrosis, and Duchenne muscular dystrophy have been mapped, efforts are underway to isolate these structural genes and to define their molecular structures. Determination of the molecular structure will enhance therapy through genetic engineering. These research activities will not be limited to single-gene disorders but will expand to enable study of the basic biology of neoplasia and, most excitingly, permit us to understand the evolutionary processes that generated the human species.

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2. Rumsby G, Carroll MC, Porter RR, et al: Deletion of the steroid 21-hydroxylase and complement C4 genes in congenital adrenal hyperplasia. *J Med Genet* 1986;23:204-209.
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Abstracts From The Literature

Gender Verification for the 1988 Winter Olympics

In 1968, the International Olympics Committee began to require that individuals taking part in women's sporting events have their female gender confirmed. This has been done by examining a buccal mucosal smear for evidence of X and Y chromatin. If a test is inconclusive, then futher testing must be done by the International Olympics Committee Medical Commission. Several recent articles have suggested that there are major technical pitfalls to the use of X and Y chromatin analysis for this purpose. This type of testing for gender is inaccurate and expensive but, just as important, does not deal with phenotypic females, such as those with 45, X0 Turner syndrome, XY gonadal dysgenesis, and androgen insensitivity syndromes in which individuals are raised as females but have negative buccal smears. Nor does it deal with XX males who have been raised as phenotypic males. Although complete genetic studies could address the technical concerns, this approach of gender verification does not deal with the psychological aspects of the individual competitors who, if they have a genetic disorder, have nevertheless been raised during their lives as members of the gender to which they have been assigned. Nor does it deal well with the competitor who intentionally wants to deceive the International Olympics Committee. It has been suggested that a simple physical examination and inspection by a physician would be less expensive and be just as accurate in establishing gender. Presumably, the intent of sex determination by the International Olympics Committee is to prevent unfair competition from a male posing as a female and using his superior muscle strength to unfair advantage. The male imposter could be easily identified by means of physical inspection, and this would appear to be less costly, more efficient, and a simpler method of gender verification.

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2. de la Chapelle A. *JAMA* 1986; 256:1920-1923.
3. Simpson JL. *JAMA* 1986;256; 1983.

Editor's comment—*The International Olympics Committee's decision to use a screening test must have arisen from an unfortunate experience. However, using an outdated, expensive, and unreliable technique to verify gender seems to be inappropriate.*

The Lawson Wilkins Pediatric Endocrine Society has addressed this issue during its annual meeting. A resolution urging appropriate athletic competition sanctioning bodies to discontinue the use of sex chromatin tests for verification of "athletic gender" and to convene an international conference of sports and medical experts to develop more appropriate and sensitive criteria to verify female gender for athletic competition was presented at the meeting; the resolution passed.

Pulsed-Field Gel Electrophoresis: A New Technique For Fractionating Large DNA Molecules

Pulsed-field gel electrophoresis for fractionating large DNA molecules is a technique that has increased the size of DNA molecules that can be separated by almost 100-fold. The development of this technique opens up the possibility of separating and analyzing pieces of DNA from 10,000 to 1,000,000 base pairs in size. The technique involves the use of restriction endonucleases that cut the DNA infrequently within the human genome. The electrophoresis is based on the rate at which these large molecules alter their shape to migrate inside the gel matrix. The technique depends on the stiff DNA molecules undergoing distortion or relaxation under the influence of the electrical field. Because there is an alternating electrical impulse, which lasts from one second to five minutes, the DNA molecules migrate in alternating fields and zigzag their way across the gel. The technique holds promise, both for isolating specific genes and for mapping the genome of various organisms.

1. Anand R. *TIG* 1986;Nov: 278-283.
2. Chu G, Vollrath D, David RW. *Science* 1986;234:1582-1585.
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Editor's comment—*Just as the Southern blot technique revolutionized DNA research 12 years ago, it would appear that this new technique represents a giant step in allowing the separation of large unique sequence pieces of DNA, both from the human genome and from other organisms.*

Transient Increases in Progesterone in Daily and 2-Hourly Saliva Specimens From Adolescent Girls

Detailed information on short-term changes in progesterone concentrations during the peri- and postmenarcheal period has been sparse because of difficulties associated with frequent collection of samples of plasma or urine. With the advent of reliable assays for progesterone concentration in saliva, Truran et al determined progesterone levels in perimenarcheal girls.

Saliva specimens were collected from clinically healthy premenarcheal and adolescent girls either daily throughout the menstrual cycle or at 2-hour intervals throughout a 24-hour period.

The mean age of the adolescents at menarche was 12 ± 1.3 (SD) years. A minority of these cycles were consistent with luteal phase (ovulatory) progesterone increases, especially within the first two years following menarche. The frequency of transient increases of salivary progesterone declined after the menarche and was negatively correlated with the first postmenarcheal year.

A large number of isolated increases (levels exceeding 150 pmol/l and preceded and succeeded by at least one sample in which levels are less than one-third those in the increased sample) were noted in the samples drawn every 2 hours from premenarcheal adolescents.

Truran PL, Leith HM, Read GH. *J Endocrinol* 1986;111:513-518.

Editor's comment—*Transient increases of salivary progesterone seem to be largely confined to the period of adolescence, with a steady decline in the rate of "spiking" in the years after the menarche. However, detailed studies in adult women (in which plasma samples were withdrawn every 10 to 20 minutes) show a pulsatile pattern of progesterone secretion in the luteal phase of the menstrual cycle. Thus, the ovary (follicle and corpus luteum) can translate the pulsatile pattern of luteinizing hormone secretion to intermittent progesterone (and estrogen) secretion.*

Salivary progesterone concentration determination represents a new noninvasive method for determining alterations in ovarian physiology. Most other steroid hormones can be determined in this fluid, and assays have been validated for cortisol, estrogens, and androgens.

In Future Issues

Catch-up and Catch-down Growth: A Review
by James M. Tanner, M.D., D.Sc.

Fetal Alcohol Syndrome
by Kenneth Jones, M.D.

Nutritional Dwarfism in Adolescents
by Fima Lifshitz, M.D.

Osteogenesis Imperfecta
by Peter Beyer, M.D.

Anabolic Steroid Hormones in Athletes: Efficacy or Fantasy?
by Alan D. Rogol, M.D., Ph.D.

Please send all correspondence to Robert M. Blizzard, M.D., Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA 22908.

Decrease in Plasma High-Density Lipoprotein Cholesterol Levels at Puberty in Boys With Delayed Adolescence: Correlation With Plasma Testosterone Levels

Kirkland and co-workers performed a three-phase study to test the hypothesis that the decrease in the high-density lipoprotein cholesterol (HDL-C) level that occurs at puberty is related to an increase in the plasma testosterone concentration. HDL-C is the fraction of total cholesterol concentration that is inversely related to the incidence of coronary artery disease.

Plasma HDL-C levels are similar in both sexes during childhood until a decrease in the HDL-C level occurs in boys around the age of puberty, with the major drop occurring between 12 to 13 and 14 to 15 years of age. Subsequently, males maintain lower HDL-C levels than do females throughout adult life.

The first phase of the study in boys (ages 10.1 to 16.9 years) with short stature, delayed adolescence, or both investigated the relationship between plasma testosterone and HDL-C. The boys were classified into four stages of pubertal development by clinical examinations (testis length and penile length). Advancing pubertal stages were associated with increasing levels of testosterone and decreasing levels of HDL-C.

In the second phase of the study, fourteen boys (ages 13.3 to 16.8 years) with constitutional delay of pubertal development were evaluated during and after treatment with testosterone enanthate. Within one to two weeks after injection, a rise in plasma testosterone levels and a concomitant decrease in HDL-C levels were observed.

The third phase of the study was designed to determine the relationship between plasma testosterone and HDL-C levels during spontaneous onset of puberty following treatment with testosterone. In thirteen subjects with constitutional delay of sexual development, the spontaneous increase in plasma testosterone levels was accompanied by a decrease in the HDL-C level.

Kirkland RT, Keenan BS, Probstfield JL, et al. *JAMA* 1987; 257:502-507.

Editor's comment—*This study provides evidence that testosterone, both endogenous and exogenous, directly or indirectly influences HDL-C metabolism during puberty. The results of the treatment phase suggest a cause-and-effect relationship between the increase in the plasma testosterone level and the decrease in the HDL-C level.*

It should be remembered that during spontaneous puberty, testosterone secretion is highly episodic only at night with significantly decreased levels during the day. Thus, the correlations noted are really underestimates of the actual physiologic condition.

These data are convincing and should allow interventional protocols to be devised to attempt to raise HDL-C in young men as "prophylaxis" against coronary artery disease.

Biosynthetic Somatomedin-C (Sm-C/IGF-I) Increases the Length and Weight of Snell Dwarf Mice

Somatomedins are thought to mediate the effects of growth hormone (GH) on body growth. However, whether Sm-C/IGF-I will also stimulate true skeletal growth (body length) and maintain the harmony of the weight/length relationship and the growth of various organs has not been determined. This study reports the effects of biosynthetic IGF-I on various growth parameters of GH-deficient Snell dwarf mice.

Groups of animals received either buffer (control), human growth hormone (hGH), or one of three doses of IGF-I three times daily for four weeks. Body length and weight were measured once a week. At the end of the study, organs were removed and weighed. Only the highest dose of IGF-I, 7.4 μg per day, was effective in increasing both the length and weight of the mice. In addition, hGH 2.8 μg/day induced significant but similar increases over controls. The relative weight of the heart of the hGH-treated mice was significantly increased, when compared to the IGF-I treated group and the controls.

van Buul-Offers S, Ueda I, van den Brande JL. *Pediatr Res* 1986; 20:825-827.

Editor's comment—*These results indicate that circulating IGF-I can lead to increased body length and weight in dwarf mice. However, they do not indicate whether this situation is physiologic, since hGH was more effective than IGF-I molar for molar. Recent results from other investigators indicate that both GH and IGF-I are important to linear growth. According to the dual effector hypothesis, GH leads to differentiation (commitment) of cells and IGF-I to clonal expansion of those differentiated to permit an orderly and efficient process of growth. The data from the present study indicate that IGF-I alone can lead to overgrowth, but they do not indicate whether this is the physiologic or most efficient mechanism of growth.*

The Rapid Ovarian Secretory Response to Pituitary Stimulation by the Gonadotropin-Releasing Hormone Agonist, Nafarelin, in Sexual Precocity

Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations reach similar maximal concentrations following a three- to four-hour high-dose infusion of gonadotropin-releasing hormone (GnRH) itself or a single maximally effective dose of a GnRH agonist. However, circulating estradiol levels in adult women usually increase within 12 to 24 hours only after the agonist injection.

The present investigation was undertaken to determine the steroidogenic response both to nafarelin, a long-acting GnRH agonist, and to an intensive standard GnRH test.

Thirteen girls with central precocious puberty were studied. GnRH was infused intravenously at a rate of 2 μg/kg/hour for 3 hours. Nafarelin was given as a single subcutaneous injection in a dose of 0.2 μg/kg. The serum LH and FSH concentrations were elevated by both GnRH infusion and nafarelin administration to reach a plateau at 3 hours. The initial rises were significantly more rapid with the GnRH analog, but only after nafarelin injection did serum LH and FSH remain significantly elevated. Plasma estradiol levels increased slightly after 3 hours with both agents, but rose 3.6-fold 24 hours after nafarelin administration.

Rosenfeld RL, Garibaldi LR, Moss GW Jr et al. *J Clin Endocrinol Metab* 1986;63:1386-1389.

Editor's comment—*A single injection of the GnRH agonist, nafarelin, sequentially stimulates pituitary and ovarian secretion in girls with precocious puberty just as early and promptly as in adult women. The pattern of steroid secretion in response to nafarelin is typical of normal ovarian follicular secretion. The ability of nafarelin to test the integrity of ovarian, as well as pituitary, function makes this compound appear useful for clinical testing.*

The gonadotropin and gonadal steroid profiles noted suggest that this compound may be useful in the treatment of precocious puberty and hormonally dependent neoplasms by long-term receptor desensitization (down regulation) of the gonadotropes.

Organ Procurement for Transplantation in Children

The number of organ transplants in children with fatal childhood diseases is increasing. Many of these disorders are either genetic or have a genetic component in their etiology. In the United States, it is estimated that there are 300 to 500 children with end-stage renal disease who could discontinue dialysis if kidneys for transplantation were available. For an additional 400 to 800 children with liver failure and 400 to 600 children with severe forms of congenital heart disease, organ transplantation is their only hope for survival. These figures do not take into account those children with inborn errors of metabolism who could also benefit from organ transplants. While the technology of transplantation has improved dramatically over the last few years, a source of tissue for organ transplantation has become a major problem. Two recent articles have addressed this problem and the ethical issues involved.

Organs from anencephalic fetuses or infants have become a potential source for transplantation. Although anencephaly is a hopeless defect of the central nervous system, the other vital organs of anencephalic infants are usually normal. It appears that fetal organs, although somewhat immature, may yield excellent results if they are transplanted, because of their ability to grow and their almost total lack of antigenicity, which makes them less likely to be rejected. However, the ethical questions involved in declaring "personhood" and death in an anencephalic infant or fetus creates some very difficult issues. First, the anencephalic fetus, for legal purposes, must be considered brain dead. Furthermore, most anencephalics are diagnosed prenatally and, therefore, are initially considered as unborn patients. However, diagnosis in the second trimester does not preclude the use of fetal organs. The usefulness of transplanting the organs from a fetal or term anencephalic depends instead on whether the organs can be maintained in a healthy condition prior to transplantation.

By defining the ethical and legal issues involved in the transplantation of organs from anencephalic infants and fetuses, investigators are making progress in an area that may affect children with a variety of genetic disorders. Another important issue is whether the cost of organ transplantation ($100,000 to $200,000) for one individual represents an appropriate use of limited health resources.

1. Harrison MR. *Lancet* 1986;ii:1383-1385.
2. Moskop JC. *J Pediatr* 1987;110:175-180.

Editor's comment—*The use of organ transplantation for children will be increasing over the next few years. Thus, it is important to be aware that anencephalics may serve as one of the important sources of healthy tissue for transplantation.*

Controlled Trial of Zinc Supplementation During Recovery From Malnutrition: Effects on Growth and Immune Function

Deficiencies of such trace minerals as zinc, iron, copper, and magnesium are often associated with protein-calorie malnutrition (PCM). To evaluate the role of zinc supplementation on growth and immune function in malnourished infants during recovery from PCM, 32 marasmic infants were randomly assigned to receive either 2 mg/kg/day elemental zinc supplement or a placebo without zinc. The marasmic condition was defined by birth weight $>$ 1,500 g, weight for age $<$ 80% WHO standard, and history of primary malnutrition without an underlying disease associated with malnutrition. All infants received a milk-based formula which provided 150 to 200 kcal/kg, 4.5 to 5.0 g protein/kg, and 3.0 to 3.5 mg zinc/day. Weight and length were measured daily; arm circumference and triceps skinfold, biweekly.

Plasma zinc and copper determinations and complete blood counts were performed at days 0, 30, 60, and 90 of the study. Function of the immune system was assessed on days 0 and 90 of zinc supplementation by cutaneous delayed hypersensitivity reaction, T-cell blastic proliferation, immunoglobulin concentrations, the number of febrile days, and the type/number of intercurrent infections. Plasma zinc and copper levels were measured serially and maintained within normal limits. They were similar in both the supplemented and placebo groups.

At 60 days, the overall gain in weight for length as a percent of standard was 9% in the supplemented group and 3% in the placebo group ($p < 0.05$). Zinc-supplemented infants had significantly fewer infectious illnesses, such as pyoderma, when compared with the placebo group ($p < 0.05$). A significant negative correlation between the plasma zinc level and the number of febrile days in the placebo group was noted during the 1- to 2-month interval ($r = 0.66$, $p < 0.05$). Following 90 days of zinc supplementation, the percentage of anergic infants had increased more than in the placebo group ($p < 0.05$). Serum IgA concentrations were greater in the zinc-supplemented group.

Castillo-Duran C, Heresi G, Fisberg M, et al. *Am J Clin Nutr* 1987;45:602.

Editor's comment—*The authors describe marginal zinc deficiency that could not be identified by plasma zinc levels, but only by salutary clinical and immunological responses to zinc supplementation.*

Zinc supplementation in these marasmic infants improved weight gain without differences in food intake and reduced the incidence of infectious morbidity. If a clinician cannot rely on standard measures to determine zinc status, ie, plasma levels, it becomes difficult to determine when supplementation is indicated and the amount required to elicit a positive response. However, mineral supplementation is recommended during recovery of malnutrition for a number of reasons. First, catch-up growth during recovery of malnutrition increases the need for zinc and other trace minerals. Additionally, diets based on cow's milk provide insufficient amounts of zinc for optimal recovery from malnutrition. Finally, marginal deficiencies of these minerals may also interfere with clinical recovery. Therefore, zinc supplementation is recommended during recovery from malnutrition since we have no other valid indication of adequate zinc levels that can permit the diagnosis of zinc deficiency in human beings. As reported in this paper, a supplement of 2 mg/kg/day is effective.

Impact of Intensive Venous Sampling on Characterization of Pulsatile Growth Hormone Release

This study applies a computer-based pulse detection algorithm to growth hormone (GH) data collected every five minutes over a 24-hour period. Previous application of this algorithm using every–20-minute sampling has demonstrated significant differences in pulsatile GH release among different groups of individuals. The present article addresses the adequacy of traditional GH sampling rates and attempts to identify the frequency of sampling necessary to capture the majority of GH pulses.

Seven adult males were studied over a 24-hour period, with sampling for GH done every five minutes. The GH levels obtained were subjected to previously published pulse detection algorithms that excluded intrinsic measurement errors influenced by unstable baselines or non-uniform peak amplitudes. In addition, the algorithm used constrains type I statistical errors to limit the rate of false-positive peaks. In this particular study, t statistics were used to constrain the false-positive rate to less than 5%.

The study demonstrates that the number of GH peaks detected is maximal with five-minute sampling, and that twice as many peaks per 24 hours are detected using sampling done every five minutes as opposed to every 15 or 20 minutes. In addition, however, in not a single case is a pulse detected with sampling done every five minutes that is not contiguous to or contained within a major secretory episode, which would have been identified by sampling done every 20 minutes. Mean GH interpulse interval is 68 minutes with sampling every five minutes as opposed to 250 minutes with sampling every 20 minutes. With less

frequent sampling there is a progressive loss of identification of high-frequency, low-amplitude GH pulses.

Evans W, Faria A, Christiansen E, et al. *Am J Physiol* 1987; 252:E549-556.

Editor's comment—*This group has previously utilized its computer-based pulse detection algorithm to describe the secretion of luteinizing hormone. The results of this study suggest that sampling every 15 to 20 minutes is optimal to detect major episodes of GH secretion, but that more intensive sampling is needed to enumerate the high-frequency GH pulsations within major secretory episodes. The physiologic and pathophysiologic significance of frequent sampling applied to subjects with growth retardation, acromegaly, protein-calorie malnutrition, and diabetes mellitus where GH secretion is abnormal remains to be shown. It is reassuring, however, that sampling every 20 minutes would appear to detect the major episodes of GH secretion and that more intensive sampling may not be required to identify most individuals with GH neurosecretory defects.*

Insulin-Like Growth Factors in Pygmies: The Role of Puberty in Determining Final Stature

Merimee and co-workers have previously shown that IGF-I levels were decreased in pygmies, although growth hormone (GH) and IGF-II levels were normal. They concluded in that study, in which they evaluated only adult pygmies and no control subjects, that short stature observed in pygmies is due to a deficiency of IGF-I. The present study evaluates pygmy children, adolescents, and adults and compares them with other African and American control populations.

Serum was obtained from 64 pygmies—33 adults, 14 children, and 17 adolescents—for determination of IGF-I, IGF-II, and IGF binding proteins. Careful pubertal staging was performed in each of the subjects, and no pygmy child was included in the study unless the parents could be identified. The control subjects were chosen to approximate the distribution of pygmies in the study according to age, sex, and maturational development.

Adult pygmies had mean IGF-I levels that were significantly lower than those of native African and American control adults. Over half the pygmy adults had IGF-I values of < 100 ng/ml, a level commonly accepted as diagnostic for hypopituitarism. IGF-II levels, however, were similar in the pygmy adults and the African control population. Mean IGF-I and IGF-II levels in pygmy children were not significantly different from those of controls, even though there was a small (but not significantly different) reduction in height between the pygmies and the African controls. This difference in height remained constant until puberty. Pygmy adolescents showed marked reductions in serum IGF-I levels, when compared to those of American adolescents, and these reductions closely mirrored the differences in growth acceleration observed during puberty. Both pygmy boys and girls had IGF-I levels that were one-third those of American adolescents. The marked acceleration in growth known to occur during adolescence in control populations was absent in pygmy boys, while a barely detectable acceleration in growth was observed in pygmy girls. Serum testosterone levels in adolescent pygmy males were within normal limits, and IGF-II was similar within all groups. All pygmies studied had normal IGF-I carrier protein patterns.

Merimee T, Zapf J, Hewlett B, et al. *N Engl J Med* 1987;316:906-911.

Editor's comment—*This study is the first to describe the absence of accelerated growth during adolescence in the pygmy population. The markedly low IGF-I levels suggest that this growth factor is the principal agent of accelerated pubertal growth. Others have demonstrated a marked increase in the amplitude of GH pulsations during puberty in normal subjects. In addition, giving testosterone to sexually infantile adolescents fails to elicit a marked rise in IGF-I in those patients who are GH deficient. Therefore, the pubertal rise in IGF-I concentration appears to depend on elevated GH levels which, in turn, are influenced by sex steroid hormone concentrations. Although the secretion of GH by traditional stimulation tests is normal in the pygmy population, Merimee and co-workers have not demonstrated a failure of GH to stimulate IGF-I during adolescence and subsequent failure of growth acceleration. Many questions remain, including the overall 24-hour integrated GH level in pygmy adolescents, identification of a possible abnormality in the GH–IGF-I axis, and identification of the hypothalamic response of normally grown subjects and pygmies to sex steroids. This very important study raises many more questions than it answers, and the reader is directed to an accompanying editorial by Rechler M, Nissley S, Roth J. Hormonal Regulation of Human Growth.* N Engl J Med *1987;316:941-943, for a discussion of the significance of these findings and the questions they raise.*

Fertility Onset, Spermatogenesis, and Pubertal Development in Male Rats: Effects of Graded Underfeeding

Manipulation of pubertal timing by undernutrition has proven to be a useful model for exploring the proposed link between this malnutritional event and the attainment of either a "critical body weight" or a "critical body fatness." Although a large body of data exists concerning the female, similar studies in males have been hampered by the lack of a discrete marker for puberty. Glass and co-workers have examined male rats given five different levels of food intake and have used the first successful conception in normal females as a marker of puberty. The effect of such graded undernutrition on the age and body weight at puberty in male rats was correlated with corresponding changes in androgens, gonadotropins, and spermatogenesis in order to shed light on the mechanism of puberty disruption in undernutrition and to clarify the relative importance of these factors in normal puberty.

All groups of rats were given the same diet, but at four levels of food intake. A group of rats on an ad libitum diet served as the control. Beginning at age 36 days, 10 animals from each group were placed each night in individual mating cages, one male per cage, each of which contained two normal females. Dates of conception were back-calculated from delivery dates of the female rats.

Eight to ten animals from each group were sacrificed after 30, 60, and 100 days on the dietary regimen. Body weight and prostate, seminal vesicle, and testicular weights were recorded along with nasoanal and tail lengths. Blood was obtained for testosterone and gonadotropin levels.

Although there was a weak inverse correlation between the age at puberty and the growth rate, the mean age at puberty did not differ significantly between the fastest and slowest growing groups. By contrast, the body weight at puberty correlated strongly with the growth rate, with the underfed rats attaining puberty at lower body weights than the normally fed rats. Underfed rats went through puberty without ever having attained the percentage of body fat that normally fed rats reached at puberty.

Androgen deficiency and low gonadotropin output induced by underfeeding were apparent as early as 30 days on the diet, and progressive adaptation was seen by 100 days. Although the male accessory organs were smaller in the underfed groups, there was only minimal impairment of sperm production. Testis histology showed mature sperm in all dietary groups at 60 and 100 days.

Glass AR, Herbert DC, Anderson J. *Pediatr Res* 1986;20:1161-1167.

Editor's comment—*This carefully designed study showed that underfeeding of male rats by as much as 70% led to minimal delay in puberty. Based on these data (and earlier data for females), for neither male nor female rats can the "critical body weight" or "critical body fat" hypotheses of pubertal timing be substantiated.*

Can these conclusions be extrapolated to human beings? It is tempting to point to the cessation of ovulatory cycles in severely undernourished females as "proving" this point, but it is more difficult to find examples among males. The sperm cycle is much longer in the human being than it is in the rat, and there is a much longer latency period between weaning and attainment of normal puberty. It would seem that undernutrition may be one of the many factors (eg, stress) that influence the human reproductive cycle and, in its severest forms, it can alter the process to the point that reproduction can be considered a "luxury" in the energy-deficient individual.

Creutzfeldt-Jakob Disease (CJD) Dura Mater Graft Association

The Centers for Disease Control reported a case of CJD in a patient who had received a dura mater graft. This is the first association between the product Lyodur, manufactured by B. Braun Melsungen A.G. of West Germany, and CJD. The product was packaged in 1982 and used primarily in neurosurgical procedures although, at times, it is used in orthopedic ear, nose, and throat, dental, urologic, gynecologic, and cardiac procedures.

CJD agent transmission has occurred in the past through contamination of corneal transplants and intracerebral electrodes, as well as with human growth hormone (GH) derived from human cadavers.

MMWR February 6, 1987

Editor's comment—*It is interesting that the CJD that developed in this patient occurred relatively rapidly following the dura mater graft. This is certainly more rapid than the incubation period observed in the children who received GH as children and developed CJD as adults. It is important to recognize that the incubation period or lag time between inoculation of the CJD agent and the development of the rapidly progressive dementing illness may not be as long as previously thought, particularly when the infectious agent is placed in proximity to the central nervous system.*

Meet the Editorial Board

William L. Clarke, M.D.

Dr. Clarke is Associate Professor of Pediatrics in the Division of Endocrinology and Diabetes at the Children's Medical Center of the University of Virginia in Charlottesville, VA. He is also Director of Student Clerkships in Pediatrics and Chairman of the Pediatric Education Council at the University of Virginia Medical School.

After graduating from Duke University in Durham, NC, Dr. Clarke attended the Vanderbilt University School of Medicine in Nashville, TN. After graduation, he served an internship and residency at St. Louis Children's Hospital, Washington University School of Medicine, in St. Louis, MO. He also became a resident-fellow at the Division of Pediatric Metabolism and Endocrinology at St. Louis Children's Hospital, where he returned after two years as a Staff Pediatrician in Endocrine-Metabolic Disease at Wilford Hall USAF Medical Center, Lackland Air Force Base, TX.

Dr. Clarke is a member of the Board of Directors of the American Diabetes Association, Virginia Affiliate. He became President of the Virginia Affiliate in 1986 after having served as Vice-President and Secretary.

Dr. Clarke has contributed extensively to the literature on endocrinology and metabolic disorders. He has authored or co-authored 36 journal and review articles, two textbook chapters, 31 abstracts, and a textbook on the subject. He has also written three practical guides for the parents of diabetic infants, toddlers, and preschoolers for the American Diabetes Association. Dr. Clarke is a contributing editor for *Behavioral Medicine Abstracts* and a reviewer for *Diabetes, Diabetes Care,* and *Pediatrics*.

James M. Tanner, M.D., D.Sc., F.R.C.P.

Professor Tanner is Emeritus Professor of Child Health and Growth at the University of London Institute of Child Health. He is also Visiting Professor of Human Growth at the University of Texas School of Public Health in Houston.

A native of England, Professor Tanner graduated from St. Mary's Medical School in London in 1944, having meanwhile attended the University of Pennsylvania Medical School in Philadelphia, followed by further training at Johns Hopkins Hospital in Baltimore.

After returning to England in 1944, Professor Tanner served as junior medical officer at the Mill Hill Emergency Medical Service Hospital (wartime Maudsley Hospital), followed by an appointment as medical officer at Southern Hospital, Dartford, Kent.

Professor Tanner then became a demonstrator in human anatomy at Oxford University, after which he joined the medical faculty of the University of London. After serving as a Lecturer and then Senior Lecturer in Physiology at the Sherrington School of Physiology at St. Thomas's Hospital, he was appointed Reader in Growth and Development at the Institute of Child Health, and later Professor of Child Health and Growth. During this time, he also served as Honorary Consultant Physician at the Hospital for Sick Children in London.

Professor Tanner was joint founder (1958) and later Chairman (1980-1983) of the Society for the Study of Human Biology, and served as Honorary Secretary of the Research Committee of the Mental Health Research Fund from 1951 to 1977. A member of the Health Services Human Growth Hormone Committee, he was Acting Chairman from 1973 to 1977. Professor Tanner is a corresponding member of the French, Swiss, Italian, Cuban, and Catalan Pediatric Societies and of the Society for Adolescent Medicine (United States).

The recipient of numerous awards, Professor Tanner received the John Alexander Memorial Prize from the University of Pennsylvania in 1986. He was named James Spence Medallist of the British Pediatric Association in 1980 and Rosen Von Rosenstein Medallist of the Swedish Pediatric Society in 1984. Professor Tanner is also a former Ernest Hart Memorial Scholar of the British Medical Association (1953) and a former Fulbright Research Associate (Jackson Memorial Laboratory, Bar Harbor, 1950).

Professor Tanner has been a visiting professor at Harvard University, The University of Chicago, and UCLA, and a lecturer at numerous institutions in the United States and Great Britain. He has written extensively on human growth and development and is the author or co-author of some 220 scientific papers and ten books, which have been translated into ten foreign languages.

MEETING CALENDAR

September 28-30 International Congress on Advances in Growth Hormones and Growth Factors Research. Milan, Italy. Contact: Drs. Daniela Cocchi and Vittorio Locatelli, Department of Pharmacology, Chemotherapy, and Toxicology, University of Milan, Via Vanvitelli 32, 20129 Milan, Italy

October 7-10 38th Annual Meeting of the American Society of Human Genetics. Town and Country Hotel, San Diego, California. Contact: Administrative Office, American Society of Human Genetics, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1825)

October 24-27 39th Annual Assembly of The Endocrine Society. San Francisco, California. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

November 13-18 Postgraduate Course—Introduction to Endocrine Investigations 1987: Techniques and Concepts. Co-sponsors: The Endocrine Society and Serono Symposia, USA. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

February 21-25, 1988 15th Annual Seminar in Pediatric Nephrology: Immunosuppression, Growth, and the Neonate. Sheraton-Bal Harbour Hotel, Miami Beach, Florida. Sponsor: Department of Pediatrics, University of Miami. Contact: Pearl Seidler, Division Coordinator, Department of Pediatrics, Division of Pediatric Nephrology, University of Miami School of Medicine, PO Box 016960, Miami, FL 33101 (305-549-6726)

July 20-23, 1988 5th International Auxology Congress. Exeter University, Exeter, England. Contact: Prof. J.M. Tanner, Room 115, Institute of Child Health, 30 Guilford Street, London, England WC1N 1EH

Growth, Genetics, and Hormones is published under an educational grant from Genentech, Inc.

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800 Second Avenue
New York, NY 10164-0569

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GROWTH
Genetics & Hormones
Vol. 3 No. 4 December 1987

Nutritional Dwarfing in Adolescents

Fima Lifshitz, M.D.
Associate Editor
Growth, Genetics, and Hormones

Introduction

Inappropriate dieting because of psychological or cultural reasons is very prevalent among adolescents.[1,2] In this era of social and dietary fads, teenagers often diet to avoid obesity or to decrease their intake of dietary fat and "junk food" or both. Inappropriate dieting, however, may result in nutritional deficiencies that interfere with normal growth and sexual maturation.[3,4] Some of the causes leading to inadequate nutritional intake among adolescents were reviewed recently.[5] Current concepts regarding nutritional dwarfing in adolescents described and reported in that review are summarized here with the permission of the authors and publishers.

Self-imposed malnutrition among adolescents is a major problem in clinical pediatric practice.[6] Usually these patients present to the pediatric endocrinologist because of short stature. They have nutritional dwarfism as defined by the Welcome Trust Classification.[7] For a variety of reasons, they voluntarily do not eat the appropriate quantity or quality of food to meet their needs for optimal health and normal growth and development. Therefore, pediatricians and pediatric endocrinologists must pay more attention to the growing number of eating disorders among adolescents and to the prevailing health beliefs and cultural influences that may determine nutritional intake.[4,5,8]

Auxology

An evaluation of the patient's pattern of growth is the most important factor in the differential diagnosis of short stature. Much attention has been devoted to the various stages of development and growth patterns of specific patients, racial groups, and populations. However, in most instances, pediatric endocrinologists and other physicians assess the stature of the patient with little consideration of changes in body weight.

Figures 1A and 1B illustrate the importance of monitoring changes in body weight in evaluating the growth pattern of a short child. As shown in Figure 1A, nutritionally-related dwarfism could not have been diagnosed without additional weight measurements throughout life. In Figure 1B, the patient's weight is seen to have decreased when he was 12 years old, and his height increments slowed concomitantly. During this period, he failed to develop sexually. His nutritional intake provided only 54% to 66% of his energy needs. He was an athletic boy who wanted to remain slim and trim. He did not have any primary endocrine or other organic disorder to account for his malnutrition. His self-imposed starvation was thought to be characteristic of *fear of obesity*, a syndrome we have described in detail elsewhere.[3]

Nutritional Short Stature—Atypical Eating Disorders

A variety of diseases, such as chronic inflammatory bowel disease, are often associated with poor growth and short stature secondary to decreased nutritional intake and malnutrition.[9] Primary undernutrition is the single most significant cause of growth retardation in countries where poverty-related food deprivation results in moderate nutritional intake and poor growth.[10] In a pediatric endocrinology practice in a suburban middle- and upper middle-class area, surprisingly, the great majority of patients with nutritional dwarfism also have no organic cause for their short stature, and there is no poverty-related malnutrition (Table). Rather, their short stature is due to self-imposed malnutrition as a result of inappropriate dietary intake. This reduced food intake may yield no significant weight loss; it merely prevents weight gain. These patients do not appear to be suffering from anorexia nervosa, since they do not engage in self-induced vomiting, strenuous exercising, or abuse of laxatives. Most seem to

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have exaggerated social concerns about obesity, and they strive to achieve and maintain an ideal slim, trim figure and eat a "healthy diet."[4]

The majority of patients with nonorganic nutritional dwarfism can only be classified as having atypical eating disorders (Table). According to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, patients with atypical eating disorders that are not otherwise specified (NOS) belong in a category reserved for those who do not fit into any of the other eating disorders (anorexia nervosa, bulimia, pica, or rumination disorder). However, we have identified three specific subgroups of patients with atypical eating disorders in accordance with primary fear or a health belief that may have caused the problem: (1) fear of obesity syndrome,[3,4] (2) failure to thrive because of specific parental health beliefs, and (3) failure to grow because of malnutrition resulting from dietary restrictions that are based on the fear of the consequences of hypercholesterolemia.[5]

Patients with NOS atypical eating disorders, as well as those in whom a more specific fear or health belief was recognized, had deteriorating linear growth and delayed sexual development, preceded by at least one or two years of inadequate weight gain. These patients did not eat enough food to allow for normal growth in the absence of organic disease. However, it should be pointed out that many of the patients observed did not undergo comprehensive psychiatric or psychological testing and, therefore, we could not be sure that subtle forms of specific eating disorders or other psychological aberrations did not exist. Nonetheless, the great majority did well, and, therefore, the presence of more severe eating disorders or gross psychiatric disease was unlikely. Moreover, catch-up growth was documented in 61% of the patients once the diagnosis of nutritional dwarfing was made and nutritional counseling and nonstructured supportive therapy were initiated. The remaining 39% had no clear-cut evidence of catch-up growth but have made progress, as has been made evident by weight increments and normal growth rates, after nutritional counseling.

Many of the patients with NOS atypical eating disorders are below the 5th percentile for height when they are referred to a pediatric endocrinologist. However, in up to one third of the patients, the stature is within the normal range, although a fall-off in height across percentiles can be documented.

Table. Nonorganic nutritional dwarfing in adolescents

	Number of patients
Atypical eating disorder	88
Fear of obesity	21
Fear of hypercholesterolemia	9
Psychosocial	2
	120

Derived from a group of 212 adolescent patients with nutritional dwarfing as the pathological cause of short stature or poor growth or both. The specific diagnostic classifications of the 120 adolescents with nonorganic nutritional dwarfing are shown. The remainder of the patients had organic causes of nutritional dwarfism, eg, chronic inflammatory bowel disease and cystic fibrosis.

Figure 1A. The patient was referred because of short stature. Initially, the heights and weights depicted in the graph were the only available data. Signs of sexual development were absent.

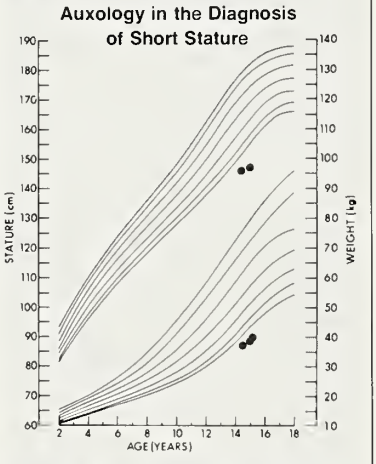
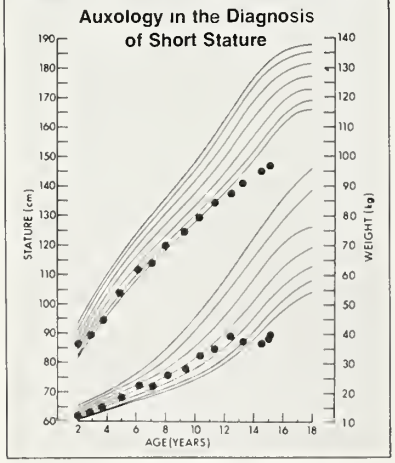


Figure 1B. The complete growth of the patient is shown. Data were obtained from school and medical records. The patient started dieting at 12 years of age to avoid obesity.



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The body weight of these patients is also below the fifth percentile, but a weight deficit for height is present in only about one half. However, a cessation or a diminution of weight increments prior to examination is evident in most patients when accurate weight records are available. A decrease in arm muscle and arm fat area may be documented, but such anthropometric alterations are not found in the majority of these patients.

The dietary intake of the patients with NOS atypical eating disorders is very similar to that found in patients with the fear of obesity syndrome.[3] They all voluntarily ingest about two thirds of the calories required for normal growth, and they frequently skip meals. Their fat intake accounts for only about one third of the calories they do consume.They avoid whole milk, red meat, and oils and other fats; most also avoid eggs. They stay away from "junk food" and have few snacks between meals. Indeed, the dietary intake of these patients resembles the prudent diet that is currently recommended by the American Heart Association.[11] While this supposedly "ideal diet" is low in fat and cholesterol, it may not provide sufficient calories and micronutrients (particularly calcium, iron, and zinc) for growth and development in adolescents. Appropriate nutritional counseling should therefore be available to all teenagers who are following low-fat, low-cholesterol diets.

The incidence of atypical eating disorders leading to malnutrition and poor growth in the general population is unknown. Only those patients whose height is markedly impaired have been recognized thus far. However, growth impaired by inadequate dietary intake and resulting in a fall-off in height within the normal percentiles may not attract medical attention. In another study, we analyzed the growth patterns of more than 1,000 upper-middle-class students attending the same high school and detected 18 students who had growth alteration associated with poor weight increments.[4,12] This finding could possibly reflect the estimated prevalence of nutritionally related growth failure in our population. However, further studies are required to ascertain the causes of poor growth in these students before we can calculate the true incidence of poor growth resulting from socially stimulated dietary restriction.

It is now known that inappropriate eating behaviors and attitudes are quite prevalent among our youth.[13] Dissatisfaction with body shape and appearance and unhealthy approaches toward weight reduction, such as fad dieting,[14] are commonly reported among adolescents. In a recent study, 13% of 10th grade students reported various types of purging behaviors, such as self-induced vomiting and the use of laxatives and diuretics.[15] We found that dieting to lose weight is very prevalent among high school students. A recent survey of high school students found that one third were on weight-loss diets on the day of the survey and that the remaining two thirds had attempted weight-reducing diets in the previous 4 to 6 weeks.[16] This occurred regardless of the body weight of the students; even those whose weight was lower than that expected for their height were concerned about dieting. The students often expressed a fear of obesity, and their distorted perception of their ideal body weight appeared to influence their actual body weight. That is, students who wanted to be thinner were indeed attaining lower weights than those who did not deliberately strive for thinness.

Iron Deficiency

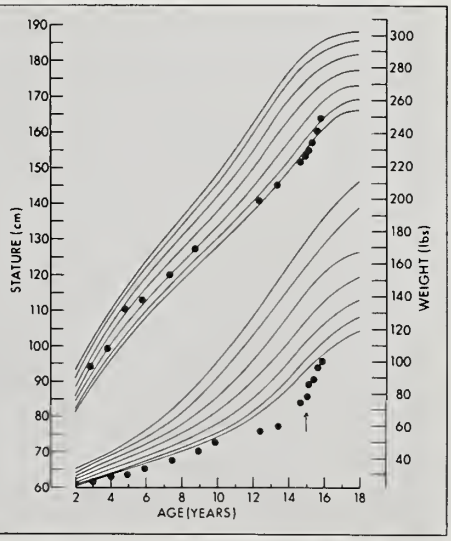
Iron deficiency is the most important nutritional deficiency in this country.[17] The incidence of iron deficiency in childhood peaks immediately after six months of age and again during early adolescence. Because iron deficiency is often associated with restrictive diets of any sort, it may be a confounding factor in the clinical evaluation of patients with eating disorders.

Iron deficiency is the end result of an imbalance between the sum of the patient's iron endowment, the intake and absorption of this element, and the sum of the patient's needs for growth and replacement of normal and abnormal iron losses. Thus, patients with failure to thrive or those with poor growth may have an iron deficiency, even though anemia may be very mild or absent. This deficiency may manifest itself as anorexia, which further complicates the eating disorder and leads to malnutrition and poor growth. Increased growth and improved appetite may occur after iron replacement.

The possible contribution of iron deficiency to poor growth and anorexia is shown in Figure 2. In this patient, iron deficiency was sec-

Figure 2. The growth pattern of a patient with an atypical eating disorder is illustrated. The main problem was anorexia. Iron deficiency without anemia was documented when the patient was first seen for nutritional rehabilitation. His hemoglobin was 13.7 g/dl, hematocrit 38.1 vol%, mean cell volume 82.7 fl, reticulocyte 2.1%. However, he had a serum iron level of 60 µg/dl, a total iron-binding capacity of 385 µg/dl with 15% saturation, and a serum ferritin level of 14.7 ng/ml despite nutritional supplements containing iron. With increased quantities of iron and appropriate supplementation, the patient gradually improved.

Iron Deficiency in a Patient With Growth Failure Due to Atypical Eating Disorder



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ondary to inadequate food intake caused by an atypical eating disorder. The clinical picture was further compounded by anorexia until the iron deficiency was corrected.

We have found that iron deficiency, usually without anemia, is common in patients with nutritional dwarfism. We saw a reduced hemoglobin level in only 12% of patients with atypical eating disorders. Only 5% had microcytosis (reduced mean cell volume level), whereas 44% had a low transferrin saturation. About one third of the patients had low serum iron or ferritin levels. In most instances, the patients achieved full nutritional rehabilitation. Thus, it is difficult to assess the exclusive role of iron deficiency in the eating behaviors of these patients. However, iron deficiency and other mineral deficiencies should be strongly suspected in patients on restrictive diets even if they do not have anemia.

A nutritional supplement containing the amount of iron ordinarily found in such formulations may not be sufficient to overcome the body's total iron deficit rapidly, particularly when the patient exhibits catch-up growth, a time when iron and other minerals are needed in higher doses.[18] Iron deficiency may continue to confound the clinical evaluation of the patient until its systemic effects (eg, anorexia) are eliminated.

General Considerations

Inadequate amounts of food and adverse environmental conditions are major problems and are the main causes of malnutrition worldwide. However, inappropriate dieting for psychological or cultural reasons may be an underrecognized problem among adolescent populations in which poverty-related malnutrition is rare. Indeed, nutritional dwarfing syndromes may be more common than other classic endocrine disorders among short-stature patients who are referred to pediatric endocrinologists. On the other hand, it should be noted that for adolescents, being slightly overweight usually carries no risk and may actually be healthier than being mildly underweight.

There are no good epidemiologic studies on the prevalence of eating disorders in the United States, but the desire to be slim and trim appears to have spread like an epidemic over the past few decades. Dieting has become a multi-million dollar industry aimed at changing an individual's shape to fit an arbitrary "thin ideal." This has occurred simultaneously with an increased stigma against obesity, as well as with the pursuit of longevity through a "healthier diet." Overweight children are regarded as "responsible" for their weight, and their failure to be thin is considered to be a sign of "personal weakness" and a lack of will power,[19] despite medical evidence to the contrary.[20]

The prevalence of dieting, inappropriate eating habits, and purging behaviors by high school students to maintain a "slim and trim figure" and to follow an "ideal diet"[13-16] is doubly alarming because it has spawned a rise in the number of patients with serious eating disorders, such as anorexia nervosa and bulimia,[21] and with other atypical eating disorders and self-induced starvation syndromes.[4,5,22] This parallels the marked decline in the consumption of red meat and dairy products that has occurred during the last decade. Sadly, many adolescents diet to attain an "ideal" figure just when they are developing and their need for adequate nutrition is high. Consequently, they become nutritional dwarfs.

Well-intentioned dietary recommendations from reputable medical sources also appear to intensify concerns and rationalizations for self-induced dietary restrictions. Consumption of foods that are high in fat and cholesterol is widely condemned by medical authorities and the media.[11] The American Heart Association, the American Health Foundation, the National Institutes of Health (NIH) Consensus Development Panel, and numerous medical authorities believe that atherosclerosis has its roots in childhood and that adherence to a prudent diet early in life will lessen the risk of this condition in later years. Thus, the medical profession may be inadvertently contributing to some of the unsound dietary practices of adolescents.

Many factors that are not necessarily tied to food or weight pervade the psychology of eating disorder patients, and these factors vary from patient to patient. Perhaps the child who is most vulnerable to social pressures to be thin is the one who adheres to a diet most strictly and, therefore, fails to grow. Perhaps he or she also has other psychological difficulties, such as poor self-esteem, feelings of incompetence, or lack of personal trust. In essence, eating disorders are a final common pathway derived from individual, familial, and cultural predisposing factors that vary in a heterogeneous patient population. In adolescents, the only visible evidence of these disorders may be poor growth.

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In Future Issues

Fetal Alcohol Syndrome
by Kenneth Jones, M.D.

Osteogenesis Imperfecta
by Peter Beyer, M.D.

Anabolic Steroid Hormones in Athletes: Efficacy or Fantasy?
by Alan D. Rogol, M.D., Ph.D.

Medical Complications of Dwarfing Syndromes
by Judith G. Hall, M.D., and David L. Rimoin, M.D., Ph.D.

Human Placental Lactogen and Fetal Growth
by Stuart Handwerger, M.D.

Erratum

The abstract "Prenatal Diagnosis of Autosomal Dominant Polycystic Kidney Disease With a DNA Probe" (Volume 3, Number 1) incorrectly stated that the disorder (adult type) had been localized to an abnormality of the short arm of chromosome 6. The abnormality is located on the short arm of chromosome 16.

Announcement

Readers of *Growth, Genetics, and Hormones* are urged to share the following information regarding the formation of the PEDIATRIC ENDOCRINOLOGY NURSING SOCIETY with their nursing colleagues.

As a professional nursing organization, PENS is committed to the advancement of excellence in nursing practice, research, and teaching in the field of pediatric endocrinology.

A stated objective of PENS is to promote communication and collaboration among all physicians and health professionals who work in pediatric endocrinology. To this end, PENS plans to:

- Sponsor an annual conference to provide continuing education for pediatric endocrine nurses
- Develop a directory of recommended patient education materials
- Generate written materials and audiovisual aids for use in patient education
- Organize a speaker's bureau of qualified nurses
- Publish a newsletter containing original articles, abstracts, and announcements
- Establish a clearinghouse for nurse and physician investigators active in clinical research
- Sponsor nursing research

Annual dues are $25; newsletter subscriptions will be available for a nominal fee. Membership applications and additional information may be obtained by writing to Pediatric Endocrinology Nursing Society, 2545 Chicago Avenue South, Suite 408, Minneapolis, Minnesota 55404. Physicians and other health professionals are invited to join as associate members.

Letter to the Editor

I read with interest Dr. Bierich's review article on constitutional delay of growth and adolescent development (CDG). He found that patients with CDG secrete less growth hormone (GH) at all stages of sexual development than do control children and suggested they have permanently diminished GH secretion.

We, on the other hand, found no significant difference between GH secretion in prepubertal children with CDG and GH secretion in controls when looking at their mean overnight GH levels, total basal GH output, total nocturnal GH pulses, mean peak nocturnal GH levels, and somatomedin-C values (Lanes et al *J Pediatr* 1986; 109:78.) Similar results were previously reported by Stubbe et al (*Ped Res* 1985;19:6). Moreover, Richter et al very recently studied a group of children with CDG and familial short stature (FSS) with the ^{15}N tracer technique and found them to have low tracer nitrogen excretion rates that were not further reduced after GH treatment; patients with GH deficiency had high tracer nitrogen excretion rates and a marked reduction of this excretion rate after GH administration. Richter et al concluded that their results yielded no evidence of partial GH deficiency in children with CDG and FSS (*J Clin Endocrinol Metab* 1987;65:74).

The variability of results so far obtained after pharmacological stimuli, as well as with measurement of spontaneous GH secretion over 24 hours or during the overnight hours, still clouds the understanding of GH secretory patterns in children with CDG, but suggests the heterogeneity of this group of patients.

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Teratogens and Growth

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Introduction

A teratogen may be defined as an agent that can produce a permanent abnormality of structure or function in an organism that is exposed during embryonic or fetal life. Teratogenic effects thus include not only such malformations as phocomelia or congenital heart defects but also mental retardation and behavioral abnormalities without gross malformation of the brain. Reduction of fetal growth per se is not considered to be a teratogenic effect.

Teratogenic agents can be divided into two classes with respect to the kind of effects they produce (Table). The first class includes agents that affect only a single organ or a very limited set of target organs in the developing embryo or fetus. Examples include masculinization of external genitalia in females (produced by exposure to androgenic hormones) and dental staining (produced by tetracyclines). Such agents would not be expected to affect fetal growth in general, and there is no evidence that they do.

The second and much larger class of teratogenic agents produces generalized patterns of anomalies. Fetal growth retardation often occurs in association with these syndromes.

Teratogens That Cause Fetal Growth Retardation

Growth retardation is a cardinal feature of the embryopathies that result from intrauterine infection by rubella, cytomegalovirus, syphilis, varicella, and toxoplasmosis.[1] The majority of newborns with clinically apparent infections due to any of these agents are growth retarded; microcephaly is frequently present. Affected individuals often continue to grow poorly throughout childhood. Similarly, exposure to high doses of ionizing radiation during embryonic development regularly leads to a permanent growth deficiency, as well as to microcephaly and mental retardation.[2]

Typical fetal alcohol syndrome occurs among the children of mothers who drink heavily during pregnancy. Growth retardation affecting length, weight, and head circumference is characteristic of this syndrome.[3] Postnatal catch-up growth is usually incomplete or absent. Fetal and postnatal growth retardation are also typical features of the embryopathy associated with maternal aminopterin or methotrexate treatment during early pregnancy.[4]

A characteristic pattern of anomalies has been observed among children born to women treated with the anticonvulsant trimethadione during early pregnancy.[5] Affected children exhibit typical facial anomalies, and congenital heart disease is frequently seen in addition to fetal growth retardation. The relationship of maternal treatment with the more commonly used anticonvulsant phenytoin to both growth retardation and the increased frequency of malformations observed among children of epileptic mothers is less clear.[6] Coumadin, polychlorinated biphenyls, and maternal phenylketonuria can also produce characteristic patterns of anomalies, including fetal growth retardation, in human beings.

Teratogens That Do Not Usually Affect Fetal Growth

Although fetal growth retardation appears to be the most consistent

Table. Classification of Some Agents With Teratogenic Potential in Human Beings With Respect to Their Effect on Fetal Growth

Class I.	**Agents that affect only a single organ or a very limited set of target organs (not associated with fetal growth retardation)**
	Maternal virilizing tumors
	Maternal lupus
	Organic mercury
	Androgenic hormones
	Diethylstilbestrol
	Tetracyclines
	Goitrogens and antithyroid drugs
	Radioactive iodine
Class II.	**Agents that produce generalized patterns of anomalies**
	Associated with fetal growth retardation
	Rubella virus
	Cytomegalovirus
	Toxoplasmosis
	Syphilis
	Varicella-zoster virus
	Maternal insulin-dependent diabetes mellitus
	Maternal phenylketonuria
	Polychlorinated biphenyls
	Alcohol
	Aminopterin and methotrexate
	Trimethadione and paramethadione
	Coumadin
	Ionizing radiation
	Not consistently associated with fetal growth retardation
	Thalidomide
	Isotretinoin
	Valproic acid

single feature resulting from exposure to known teratogens in human beings,[7] the relationship between teratogenesis and fetal growth retardation is neither simple nor constant. Some agents with unequivocal multisystem teratogenic potential in human beings do not seem to affect fetal growth substantially. Isotretinoin is a good example. Maternal ingestion of this vitamin A analog early in pregnancy can produce serious craniofacial, cardiac, central nervous system, and thymic malformations in the offspring.[8] However, among 21 affected infants, only two were small for gestational age. This is exactly the number expected in the general population. Similarly, growth retardation does not appear to be a common feature of thalidomide embryopathy.[2]

Agents Without Significant Teratogenic Risk That Affect Growth

Intrauterine exposure to certain other agents clearly reduces fetal growth but does not appear to be associated with measureable teratogenic effects. Maternal cigarette smoking during pregnancy is not considered to be teratogenic, but it clearly causes fetal growth retardation.[3,9] Low birth weight is twice as frequent among the infants of smokers as among the infants of nonsmokers. Birth length, and possibly head circumference, is also affected. In general, the more a pregnant woman smokes, the more likely her infant is to exhibit growth retardation. Postnatal catch-up growth in children of cigarette smokers may not be complete.

Infants born to women with such infections as hepatitis B, influenza, and listeriosis may exhibit growth retardation, as well as manifestations of the infectious disease, but malformations are usually absent.[1]

Fetal exposure to low doses of agents that are teratogenic at high doses may result in growth retardation only. For example, pregnant women who drink alcohol in amounts far below those associated with the occurrence of fetal alcohol syndrome may, nevertheless, be at increased risk for having a growth-retarded infant. Significantly, reduced birth weight has been observed among the children of women who drank as little as 1 1/2 to 3 ounces of alcohol a day during pregnancy.[10]

Common Pathogenic Mechanisms

Since agents may cause fetal growth retardation in circumstances under which they are not teratogenic, and since some human teratogens do not cause growth retardation, it seems unlikely that these are different aspects of a single phenomenon. The frequent association of fetal growth retardation with teratogenesis suggests, however, that common mechanisms might underlie both processes.

In considering what these mechanisms might be, it is important to recognize that both fetal growth retardation and teratogenesis are pathogenically heterogeneous. Even for growth retardation occurring in association with congenital infections due to the so-called "TORCH" agents, underlying mechanisms are diverse.[1] Cytomegalovirus causes tissue injury as a result of cell lysis, as well as vascular perfusion by damaging capillaries and small vessels. Decreased cell numbers and decreased mitotic activity occur in congenital rubella syndrome, but these may be a consequence of vascular damage. In congenital syphilis, fetal growth retardation may be caused by placental dysfunction resulting from the edema and inflammation of syphilitic placentitis.

Many processes are involved in normal embryogenesis, and interference with any of these could produce a teratogenic effect. Cell death or altered cell growth and proliferation may mediate the teratogenic effect of ionizing radiation, for example, and these factors could also impair growth of the entire fetus. Disturbed tissue interaction, defective cell or tissue migration, mechanical or vascular disruptions, and disordered programmed cell death could also lead to teratogenic lesions, but the effects of such processes on the growth of the embryo as a whole are likely to be indirect. Such indirect effects on growth could, nevertheless, be quite important. It is easy to imagine, for example, how failure of induction of critical metabolic processes or failure to form a structurally normal placenta could adversely affect cellular nutrition and thus overall growth in the embryo or fetus.

Clinical Recognition of Growth Retardation Due to Teratogenic Agents

In theory, recognition of fetal growth retardation due to teratogenic agents should never present a problem, because there should always be a history of maternal exposure to the agent during pregnancy. In practice, however, this history is often not available, at least initially, for several reasons. In some instances, the mother was unaware of the exposure. This is frequently the case with cytomegalovirus or toxoplasmosis infection. However, even when an exposure is recognized, neonatal or obstetrical records may not reflect it, especially in the case of commonly-used agents, such as alcohol, in moderate amounts. Moreover, women often report exposure only from the time the pregnancy was recognized. Thus, much of the critical period in terms of teratogenic risk may have already elapsed. Therefore, in evaluating a neonate with growth retardation, it is necessary to take a thorough history directly from the mother regarding possible exposure to infectious and environmental agents, drugs, alcohol, and tobacco since the time of conception.

The second aid to clinical recognition of teratogen-induced growth retardation is that the teratogens that cause growth retardation are also those that produce characteristic patterns of anomalies. In the embryopathies associated with alcohol, aminopterin, coumadin, and the "TORCH" agents, the dysmorphic features

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Teratogens and Growth
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are often sufficiently characteristic to suggest the diagnosis even in the absence of a history of maternal exposure. A thorough examination of major and minor dysmorphic features should be performed on every child with fetal growth retardation. Children found to have associated anomalies should be referred for evaluation by a clinical geneticist or dysmorphologist.

Importance of Recognizing Growth Retardation Due to Environmental Agents

Epidemiologic studies suggest that as many as 40% of cases of fetal growth retardation may be associated with maternal cigarette smoking alone or in combination with other factors.[11] Other environmental agents appear to be uncommon causes of fetal growth retardation, but the effect of maternal "social" drinking has not been adequately evaluated in this regard. Even if growth deficiency due to teratogenic agents is relatively uncommon, the recognition of this group of children is especially important because they are more likely to have failure of catch-up growth, developmental delay, and associated malformations. Growth retardation due to teratogens is also especially important from a public health perspective because teratogen exposures are often potentially preventable.

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Catch-Up and Catch-Down Growth: A Review

James Tanner, M.D., D.Sc.
Associate Editor
Growth, Genetics, and Hormones

Growth in children is never consistent. Small variations occur seasonally. Frequently, significant alterations occur with illness, nutritional failure, the administration of exogenous hormones, or the increased production of endogenous hormones. Following significant alterations in growth, compensatory catch-up or catch-down growth frequently occurs. This topic has been poorly understood. The goal of this article is to provide an update on current concepts.

Catch-Up Growth

Under normal circumstances, a child's increase in height follows a very regular path, if considered over periods of a couple of months or more. So regular is it, indeed, that the rate of such growth is one of the best indices of a child's general health. Minor illnesses cause minor irregularities: Rogers[1] fitted Preece-Baines curves[2] to the heights of individual children followed longitudinally in the Harpenden Growth Study and found that the deviations from the curve were greater in those children who had many episodes of minor illness than in those who had only a few. Such illnesses were not associated with lower adult heights or even with reduced growth velocities considered over a year or more. Nevertheless the children were nudged off course temporarily.

When the interruption of growth has been great, the restoring force is also great, and when the failure is repaired, the child springs forward to catch up to his previous growth curve. As he approaches his genetically predisposed channel, the restoring force diminishes, and the child's growth slows down and proceeds as smoothly as before. At least this is what happens in the most favorable circumstances, eg, juvenile hypothyroidism, where catch-up is almost always complete, provided treatment starts before the child is about 14 years of age.[3] In less favorable circumstances—eg, children who are admitted to the hospital with kwashiorkor and then returned to a family environment characterized by semi-starvation—the catch-up growth may be only partial.[4] In children with growth hormone deficiency (GHD) who are treated with growth hormone (GH), as illustrated in Figure 1, striking initial catch-up growth occurs with treatment (14 cm/year in the first six months of treatment). However, full restoration to genetic potential, as represented by the parental target height range shown in the upper right part of Figure 1, may not occur in the long run.[5] Perhaps the difference between the extent of catch-up growth in children with thyroxin deficiency and those with GHD is rooted in the much greater delay in bone age that occurs in hypothyroidism, or perhaps it is simply that the child with GHD has fallen much further below the normal percentiles for age than usually occurs in hypothyroidism.

In examining the final height of 30 boys with idiopathic isolated GHD who were treated continuously with human growth hormone (hGH) until growth ceased of its own accord, Burns et al[6] found

December 1987

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that only the standard deviation (SD) score for height at the beginning of treatment (with allowances made for parental heights) was important. The lower the SD score initially, whatever the child's age, the lower the final height, by some 2.5 cm for each SD score below the mean for the group. Of the 6 SD lost by untreated GHD patients before GHD was recognized, we were able to restore 4 SD on average, but we were not able to restore the other 2 SD. This was true even in patients who received treatment as early as four years of age.[7] In those first few years of rapid growth, a deficit that is only partly recoverable seems to accumulate. We do not know why this is so.

Catch-Down Growth

Catch-down growth is the opposite of catch-up growth. If growth is artificially stimulated and then the stimulating force is withdrawn, the growth velocity drops for a while, as shown in Figure 2. We need a term for this phenomenon, and none has been forthcoming. "Compensatory deceleration" has been suggested. The term "catch-down," however, originally suggested as a linguistic joke, seems to have caught on. Not all children treated with GH exhibit this marked deceleration in comparison with pretreatment growth rates. The reason for the differences between children remain obscure.

Catch-Up and Catch-Down as Normal Occurrences

In infancy, catch-up and catch-down growth occur as normal phenomena. Soon after the longitudinal data for growth from birth to maturity became available, it was shown that the correlations between measurements taken in an individual child at various ages—birth, one month, three months, six months, and so on—and his or her measurements as an adult had a characteristic temporal pattern. The correlation between length at birth and adult height was low (approximately 0.3). By six months, the correlation coefficient had risen to 0.5; by one year, it had risen to 0.7; by two years the stable prepubertal value of 0.8 was reached. Thus, during infancy a reassortment of relative sizes among children comes about: Those who are larger at birth grow less; those who are small grow more. Figure 3, from an old but comprehensive study,[8] illustrates this. It should be noted that the velocity curves for weight of only the extreme birth weight cohorts of 5 to 6 lbs and 9 to 10 lbs are shown. In a classic paper, Smith et al[9] described the same thing in American middle-class, well-nourished babies.

In fact, the curves shown in Figure 3 conceal heterogeneity. Not all 9-pounders grow especially slowly, only those whose genes specify an average adult size but whose maternal uterus was highly stimulatory. Some of the 9-pounders come by it honestly: large at birth and large later. But the others slow down until they hit their proper curves. Likewise, the small

Figure 1. Partial catch-up growth in a boy with idiopathic isolated growth hormone deficiency treated with growth hormone.

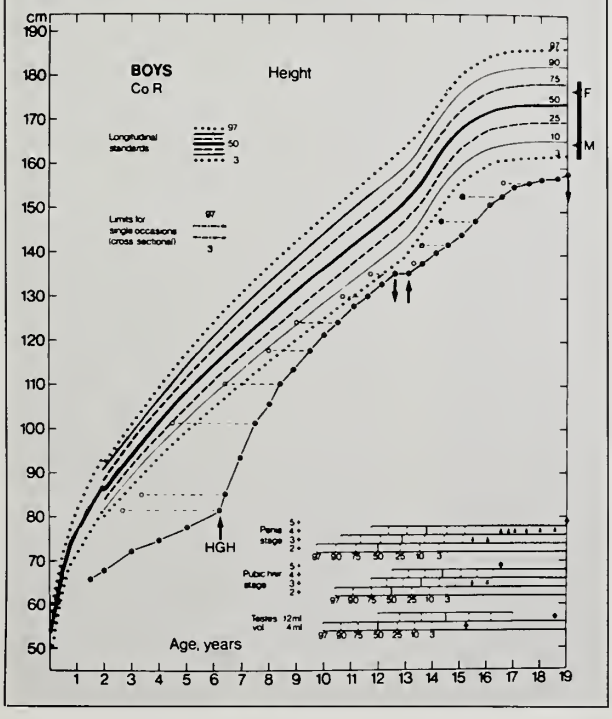
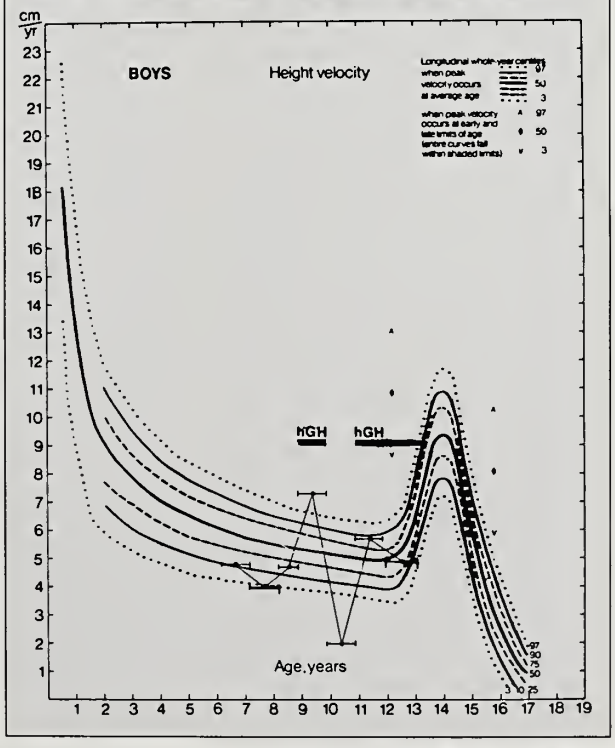


Figure 2. Catch-down growth in a patient receiving growth hormone on two occasions separated by a year without treatment. The growth velocity off treatment is significantly lower than the pretreatment velocity. The growth velocity on treatment also wanes with extended treatment.



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Catch-Up and Catch-Down Growth

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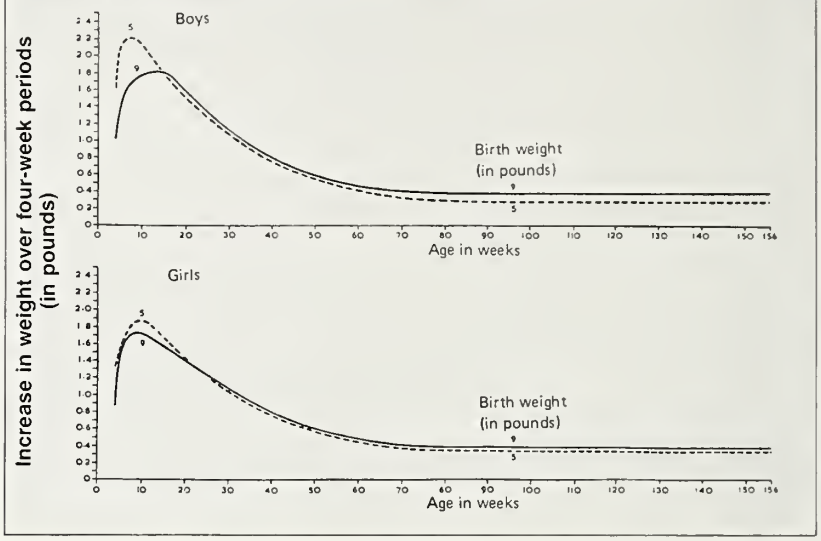
babies with genes for average final height catch up to their proper curves, a process usually completed by about 12 months. This was already well known to animal breeders: If a large Shire horse is crossed with a small Shetland pony, the size of the newborn foal closely follows the size of the mother.[10] But the tiny foal of the Shetland mother has half of its height-determining genes from its great Shire father, just as the large Shire-mother foal has genes from its small Shetland father. After a few months, the two foals are nearly the same size.

Figure 3. Weight velocity curves of cohorts of babies weighing 5 to 6 lbs and 9 to 10 lbs at birth. As a group, the smaller infants grow more rapidly than the larger infants.



The Mechanism of Growth Regulation

Catch-up and catch-down growth are simply exaggerated forms of normal growth regulation. We do not know how the extraordinary precision of growth is maintained or how it is, for example, that monozygotic twins who differ by 3 cm in length at birth grow so that there is only a 1-cm difference in adult height. We do not even know how the normal rate of growth is established or why the velocity of growth in general diminishes as a child gets older. When we fit curves to the growth of individuals, we use equations, nearly all of which assume that growth velocity at any time is a function of the *remaining* growth or, what is the same thing, the percentage of height completed. But how does the child "know" what percentage he has attained?

Many years ago, I suggested a "central" model to explain this,[11] but "peripheral" models are also possible. In the central model it is supposed that some sort of "sizostat" exists in the central nervous system; the sizostat tells the animal what size it "ought" to be at each moment during its growth. The sizostat could do this by synthesizing and/or releasing every so often, for example, a specific molecule not yet identified. The rate of synthesis would decrease theoretically as maturity increases. If this is true, there must be another signal that tells the animal what size it actually *is*, perhaps by synthesizing another series of molecules, this time in strict proportion to the amount of growth. Theoretically, these molecules would enter the central nervous system to interact with the size-stuff and bind to it so that only a certain amount is left. This remaining amount is the mismatch signal that controls the output of growth-stimulating hormone.

Recently, Mosier and his colleagues[12-14] designed experiments to test this model. If rats have their heads irradiated shortly after birth, their subsequent growth will be stunted. If tested later, after a 48-hour fast, their capacity for catch-up will not be impaired; they catch up to their control-irradiated curve but not to a normal-control curve. The catch-up of normal rats starved for 48 hours is associated with an increased amplitude but not frequency of GH pulses, especially during the light part of the light-dark cycle. Although the irradiated rats secrete a little less GH than do normal rats during both their control and catch-up growth, this does not necessarily mean the difference in GH secretion is causative. Mosier thinks otherwise: The control resides in a sizostat, which the irradiation has damaged. This is the explanation I gave for the seemingly unalterable short stature of children with early intrauterine lesions (eg, Silver-Russell syndrome). Mosier has very recently localized the effect of head irradiation to the midline structures, probably the suprachiasmatic nucleus.

This model may, of course, be erroneous since the evidence is far from conclusive. Perhaps all regulation takes place in the generative and proliferative layers of cartilage, with each cell having its intrinsic rhythm of division and gathering a greater need to divide the longer it lacks the necessary local hormone to do so. However this may be, the physiology of normal growth control is clearly the key to understanding catch-up and catch-down growth, as well as the effect of the various therapeutic interventions now being used or considered for the treatment of all sorts of short stature.

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Special Report:
International Growth Hormone Symposium—June 15-18, 1987, Tampa, Florida

Robert M. Blizzard, M.D.
Chairman, Editorial Board—Growth, Genetics, and Hormones

Dr. Barry Bercu (Tampa, Florida) was the primary organizer of this excellent conference. Because a great deal of material, much of it complex, was presented, this summary highlights only the major points that were covered.

Neuroendocrine regulation of growth hormone (GH) secretion received considerable attention. Drs. Gloria Tannenbaum and Joseph Martin demonstrated very convincingly that GH-releasing hormone (GHRH) is secreted in the posterior part of the hypothalamus (tubero-infundibular region) and that growth hormone-releasing factor (GRF) is secreted in the ventromedial and arcuate nuclei. Somatostatin neurons are located primarily in the anterior hypothalamic region.

Galanin is a recently described neuropeptide of 29 amino acids; its action is additive to that of GRF. Galanin is produced in the ventromedial and arcuate nuclei, and the action is blocked by somatostatin. Dr. Eugenio Muller (Milan, Italy) emphasized that epinephrine is necessary for GH to be released by galanin. Dr. Muller also emphasized the importance of the cholinergic system and demonstrated that GH release in response to exercise, arginine, and clonidine is blocked by atropine. Clonidine, an alpha$_2$ adrenergic agent, was used by Muller and his co-workers to increase GH production and increase growth velocity over six- and 12-month periods in at least some children with severe short stature.

Dr. Alan Rogol presented data obtained from 20 patients who were treated with GRF in an international collaborative study. Dr. Rogol stated, "A more potent analog is needed if GRF is to be a valuable therapeutic agent." However, GRF remains a very valuable study tool for those interested in neuroendocrine interrelationships.

Dr. John Phillips discussed the presence of the two GH and three HCS genes on chromosome 17. Recently, a placental GH (derived from the hGH-V gene) has been described. This is a 22 K pituitary GH with 13 substitutions. A poster submitted by Frankenne et al demonstrated that GH was not present in amniotic fluid or in fetal serum. This produced some skepticism regarding the possible role of this hormone as a fetal GH. Dr. Phillips indicated that the first CMS gene is inactive and that apparently none of the GH or HCS genes are necessary for survival.

Drs. Gerald Baumann and James Lewis discussed the various forms of monomeric hormone in the pituitary and in serum. The human growth hormone (hGH)-N gene is responsible for production of both 22 K and 20 K GH. The latter has minimal immunologic and growth-promoting activity, but does have diabetogenic activity. Dr. Lewis concluded, "Although the number of GH variants and modifications have reached eight, there are at least an equal number of unidentified forms in pituitary extracts." A most intriguing part of Dr. Baumann's presentation was his description of two binding proteins for GH found in plasma. The function of these binding proteins remains unknown, but there is some indication that one or both of these proteins could be receptor related and that even a partial portion of the receptor passed into the serum.

Dr. Hiroo Imura described a highly innovative sandwich enzyme immunoassay to measure GH. The assay's lower limit of sensitivity equals 50 pg/ml. Since GH is found in nearly all normal individuals at all times, Dr. Imura utilizes this assay, which he developed with his co-workers, in diagnosing GH deficiency and acromegaly. Using this technique to measure GH in urine enhances its diagnostic capability. Dr. Imura also determined that the kidney plays an important role in the degradation of GH.

Several experts discussed human insulin-like growth factor (IGF)-I and IGF-II. Dr. Matthew Rechler and others are exploring the possibility, which seems more likely to be a probability, that IGF-II plays a role in fetal growth. Drs. John Sussenback and Michael Czech discussed the role of the IGF-II gene and receptors, respectively, in the fetus and the neonate. Their data tend to substantiate an important role for IGF-II in fetal growth.

Drs. Olle Isaksson, Rudolf Froesch, and Naomi Hizuka individually presented data comparing the effects of GH and IGF-I on skeletal growth. IGF-I, as dem-

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Special Report:
International GH Symposium
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onstrated by Hizuka and Froesch, has a growth-promoting effect on the tibial plates of hypophysectomized rats. Isaksson infused GH locally on one of the epiphyseal plates, that of the right femur, and demonstrated unilateral growth in that femur. His thesis is that GH stimulates colony formation of epiphyseal chondrocytes adjacent to the epiphysis, while IGF-I stimulates cells isolated both in the proximal and intermediate parts of the growth plate.

Dr. David Clemmons studied the metabolic action of GH in relation to nutrition and reported that IGF-I levels do not fall in obese individuals with low energy diets; they do fall in individuals who are not obese. Their preliminary data suggest that administration of GH at 0.1 IU/kg body weight every other day does not enhance weight loss in obese individuals.

Dr. Kerstin Albertsson-Wikland presented data suggesting that integrated concentrations of GH are directly proportional to the height of children both in pubertal and prepubertal stages. Dr. Barry Bercu recapitulated his extensive studies of short children with regard to GH concentrations in serum over 24 hours.

GH neurosecretory dysfunction was discussed extensively. Most agreed that this is an appropriate term for patients who have been exposed to cerebral irradiation and who have dysfunction of GH secretion. However, many investigators are not ready to apply the term to other entities in which there may be diminished GH secretion.

Dr. Raphael Rappaport studied the effect of cranial irradiation on GH secretion and growth in a large number of patients and reported that slowing of growth usually does not occur until at least 18 months after brain irradiation. Patients receiving spinal plus cranial irradiation have greater limitation of growth potential than do those who receive cranial irradiation alone.

Those interested in purchasing a copy of the published proceedings of this conference should contact Dr. James Posillico of Serono Symposia USA at 800-225-5185.

Special Report:
Annual Meeting of the American Pediatric Society/Society for Pediatric Research (Genetics Sessions)—April 27-30, 1987, Anaheim, California

Judith G. Hall, M.D.
Associate Editor—Growth, Genetics, and Hormones

Among the highlights of this meeting was the awarding of the outstanding young investigator prize to Dr. Arthur L. Horwich for his work on the molecular structure of ornithine transcarbamylase. The gene was isolated and sequenced and found to have three sections: a leader peptide necessary for directing the molecule into the mitochondria, a propeptide section requiring removal to activate the enzyme, and the enzyme itself. Using in vitro mutagenesis, Dr. Horwich was able to identify the amino acid sequences that led to changes in the various parts of the protein.

Dr. D.S. Rosenblatt reported a new vitamin B_{12}-dependent condition in which mild retardation is associated with megaloblastic anemia. The condition is responsive to vitamin B_{12} therapy.

Studies of ovarian function in galactosemic patients conducted by Dr. Francine Kaufman and her colleagues indicate that females who were completely deficient in galactose-1-phosphate uridyl transferase all had ovarian failure. Only those galactosemic patients with partial presence of the enzyme were fertile.

Dr. Ian T. Thomas reported a large number of patients with chromosomal mosaicism that was not necessarily reflected in the karyotypes of the peripheral blood cells. Mental retardation, asymmetry, and striking pigmentary abnormalities, however, were present. Dr. Robert Brent reported that antiserum against yolk sac proteins could have a teratogenic effect and that this effect could not be reversed by vitamin supplementation. Dr. Ira Chasnoff confirmed previous reports that cocaine use by pregnant women is associated with genitourinary tract anomalies in the fetus.

In his paper on Rett's syndrome, Dr. John Moeschlen said that the disorder is much broader in spectrum than had been previously recognized.

Dr. Grant Mitchell isolated a gene and at least two pseudogenes connected with the ornithine aminotransferase deficiency that may account for gyrate atrophy. Cytogenetic molecular studies of non-disjunction in trisomy 13 syndrome, which were reported by Dr. Terry Hassold, indicate that 60% to 70% of non-disjunction occurs in the first maternal meiotic division, just as it does in Down's syndrome. Molecular studies by Hassold et al demonstrated that, because of lack of crossing over, non-disjunction did not occur. Dr. Carolyn Hadley described experiments in which the gene for phenylketonuria was transferred into hepatocytes via a retrovirus. In his presentation, Dr. Aubrey Milunsky reported that the serum alpha-fetaprotein determination used to screen for chromosome defects was as efficient when used in the first trimester as it was in the second.

Special Report:
Annual Scientific Meeting of the American Diabetes Association—June 6-9, 1987, Indianapolis, Indiana

William L. Clarke, M.D.
Associate Editor—Growth, Genetics, and Hormones

The plenary sessions of this annual meeting included symposia on lipid metabolism, insulin action, and the mechanisms and management of diabetic neuropathy. The Banting Memorial Lecture, given by Dr. Joseph Larner (Charlottesville, Virginia), concerned insulin signaling mechanisms.

Several papers that were presented are of particular interest to those who are studying growth. MacGorman (Rochester, Minnesota) presented a paper on the importance of growth hormone in the maintenance of basal lipolysis in normal man. Using a study design in which somatostatin, insulin, glucagon, and glucose were infused in amounts necessary to maintain euglycemia, MacGorman et al infused labeled glucose and palmitate into seven normal human volunteers. Human growth hormone (hGH) was then administered either by constant infusion or by hourly boluses. When hGH was administered in a pulsatile fashion, palmitate levels were higher than when hGH deficiency was induced. However, no differences in glucose metabolism were observed. These results indicate that hGH is important in the maintenance of basal lipolysis during the night in normal volunteers and that free fatty acid metabolism may be more sensitive than glucose metabolism to hGH.

Jacob (New Haven, Connecticut) presented a paper entitled "Effect of IGF-I to Lower Blood Glucose and Its Effect on Hepatic Glucose Production." In this study, fasted rats were infused with either saline or recombinant human IGF-I (THR59) while simultaneously being infused with tritiated glucose; these infusions were done to determine hepatic glucose production. It was demonstrated that IGF-I produced hypoglycemia in rats by selectively enhancing peripheral glucose uptake. Liver glucose metabolism was relatively unresponsive to IGF-I in comparison with insulin, which suggests that IGF-I and insulin affect hepatic glucose production by different cellular mechanisms.

In a paper entitled "Diabetes Mellitus Influences Growth by Regulating Hepatic Insulin-Like Growth Factors I and II Gene Expression," Yang (Madison, Wisconsin) compared the effect of streptozotocin-induced diabetes on the growth rate of young rats and on the transcription and translation of IGF-I and IGF-II. Although serum IGF-I levels correlated positively with hepatic mRNA and negatively with blood glucose concentrations, neither relationship held for IGF-II. Yang et al concluded that hepatic IGF-I mRNA, serum IGF-I levels, and growth rate are decreased by poorly controlled diabetes and are normalized by insulin therapy. In contrast, IGF-II synthesis and release are only slightly altered, suggesting that this somatomedin is less important in growth regulation.

Two papers concerning GH and diabetic retinopathy were presented. The first, by Shumak et al (Toronto, Ontario), was entitled "The Effect of Growth Hormone Suppression on Established Preproliferative Diabetic Retinopathy." Four Type I diabetics with preproliferative retinopathy and varying degrees of macular edema received eight weeks of therapy with a long-acting somatomedin analog (SMS 201-995). Glycosylated hemoglobin bA_{1c} concentrations did not change during the study, while 24-hour integrated GH concentrations declined by about 42%. Visual acuity improved in all eight eyes but was not associated with detectable morphologic changes on stereofundus photography or fluorescein angiography. Within two months of discontinuing analog treatment, visual acuity returned to pretreatment levels. The mechanism by which visual acuity improved is unclear, although subtle changes in the degree of macular edema may have occurred.

The second paper, presented by Sundkvist (Sweden), was entitled "Absent Elevations in Growth Hormone and Endothelial Factors During Exercise Predict a Resistance Against Retinopathy." Plasma levels of GH, endothelial factors, and GH factor VIII-related antigen, and plasminogen activator activity were recorded during exercise in 22 patients with insulin-dependent diabetes. The patients were reevaluated five to seven years later for the absence or presence of retinopathy in relation to previous exercise test results. Patients with retinopathy at follow-up showed significant elevations in GH factor VIII-related antigen and plasminogen activator activity during exercise. In contrast, patients without retinopathy at follow-up did not show significant elevations of these values during exercise. Sundkvist et al concluded that the absence of elevations in GH and endothelial factors during exercise may predict resistance against retinopathy in patients with insulin-dependent diabetes mellitus.

Further information regarding these and other papers concerned with growth can be found in *Diabetes* Vol. 36, Supplement I, 1987.

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Growth in Turner's Syndrome: Long-Term Treatment With Low-Dose Ethinyl Estradiol

The use of low-dose estradiol (100 ng/kg/day) was previously reported by Ross et al (*N Engl J Med* 1983;309:1104) to increase the growth rate of patients with Turner's syndrome after six months of treatment. In this study, Martinez et al attempted to reproduce and extend the studies of Ross et al.

Nine patients with Turner's syndrome between the ages of 8.6 and 13.3 years were treated with ethinyl estradiol, 100 ng/kg/day, for 18 months. The growth rates increased in all nine patients during the first six months of treatment (3.09 cm/yr ± 1.05 *v* 7.09 cm/yr ± 1.47), but fell progressively during the 6th to 12th months (6.08 cm ± 1.78) and the 12th to 18th months (4.03 cm ± 1.65). The bone ages increased by more than two years in six of the nine patients during the 18 months of treatment (from 9.23 ± 1.60 to 11.63 ± 1.27), and the predicted heights did not change.

The integrated concentrations and the number of peaks of GH observed during a seven-hour period (07:30 to 14:30) did not change, as was the case for IGF-I levels as determined by both bioassay and radioimmunoassay. The predicted heights also did not change.

Sexual development was noted during the first six months of treatment in all patients, but regression occurred in seven patients over the next 12 months.

The authors conclude that growth velocity is increased with this regimen but ultimate height is probably not affected.

Martinez A et al. *J Clin Endocrinol Metab* 1987;65:253.

Editor's comment—*The patients in this study have been treated with estrogen longer than those in any other study reported to date. The effect of oxandrolone alone, growth hormone (GH) alone, and both together also has resulted in increased growth over a 12-month period (*J Pediatr *1986;109:936-943). My personal observations using oxandrolone over the years are that growth rates return to their low levels by the third year of treatment. Will oxandrolone or GH or both increase ultimate height when used over an extended period? The answer to this question will not be known for several years.*

RMB

Testosterone Treatment of Constitutional Delay of Growth and Development: Effect of Dose on Predicted Versus Definitive Height

Boys with constitutional delay of growth and adolescent development (CDGAD) are treated with different hormones or anabolic steroids or testosterone or a combination of the three. In adolescents, testosterone is favored, since it stimulates both growth and sexual development. While there is no doubt about the short-term success of such treatment, opinion regarding the long-term effects is divided, particularly with respect to ultimate height.

Martin et al carried out a large longitudinal study on 44 adolescents with CDGAD who received different doses of testosterone enanthate. A group of 14 untreated boys with CDGAD served as controls. The inclusion criteria for the study were pretreatment growth velocity less than 4.0 cm/year, height less than the 5th percentile, retarded puberty (P_1 or P_2), and a delay in bone age corresponding to that in height. Treatment was started when the boys were 14 or 15 years of age. Group I received 200 mg testosterone enanthate monthly, group II received 100 mg, and group III, 50 mg. During a year of continuous treatment, the growth velocity advanced considerably in all treated groups (10.9 cm ± 0.5 cm in group I, 11.0 cm ± 0.6 cm in group II, 10.7 cm ± 0.4 cm in group III). The ΔBA/ΔHA ratio was 2.0:1.8 in group I, 1.8:1.7 in group II, and 1.5:1.5 in group III. In the year after the discontinuation of therapy, the growth rates dropped—most markedly in group I (4.6 cm/year), less in group II (5.0 cm/year), and least in group III (7.0 cm/year). This led to a statistically significant loss of ultimate height in group I. Measured adult height in these patients was 167.8 cm, or 3.3 cm less than the predicted ultimate heights that were calculated at the start of treatment according to RWT. No significant differences were seen between predicted and measured adult height in groups II and III.

Martin MM, Martin ALA, Mossman KL. *Acta Endocrinol* 1986; 279(suppl):147-153.

Editor's comment—*This study of a fairly large number of patients brings about important, statistically ascertained results. With testosterone treatment, the desired and expected growth spurt occurs in all three treatment groups. However, in the year after treatment, a rebound phenomenon occurs, which depresses the gain in height age to 0.7 years/year and leads to a significant loss of ultimate height. In light of these results, long-term therapy with 200 mg testosterone per month is certainly contraindicated. On the other hand, treatment with 50 mg testosterone per month provides satisfactory results and is free of undesired side effects as well.*

JRB

Short-Term Metabolic Effects of Recombinant Human Insulin-Like Growth Factor (IGF-I) in Healthy Adults

Recombinant human IGF-I was administered intravenously (IV) at a dose of 100 μg/kg to eight healthy adult volunteers after a ten-hour fast. In addition, on a separate day, 0.15 U/kg of IV insulin were administered to the same subjects. Serum was obtained after the fast and after each injection for determinations of total and free circulating IGF-I, glucose, growth hormone (GH), cortisol, lactate, epinephrine, norepinephrine, glucagon, and free fatty acids.

The mean fasting blood glucose level was 4.65 ± 0.30 mmol/l. Similar reductions in blood glucose were observed with either IGF-I or insulin (1.98 ± 0.44 and 1.78 ± 0.29 mmol/l, respectively, 30 minutes after injection). Blood glucose levels returned to 3.50 ± 0.56 and 3.48 ± 0.25 mmol/l within 120 minutes of IGF-I and insulin administration, respectively. The glycemic curves for those studies were not significantly different. Serum IGF-I rose from 144 ± 38 ng/ml to 424 ± 56 ng/ml 15 minutes after administration and fell to 261 ± 56 ng/ml after 60 minutes and remained at that level for seven hours. Serum levels of free IGF-I rose within 15 minutes after injection from 26 ± 8 ng/ml to 343 ± 87 ng/ml and then decreased to its initial value within seven hours. Blood glucose values returned to normal after two hours, although total IGF-I was still elevated. Peak GH values were reached at 45 minutes (19.3 ± 9.4 ng/ml) after IGF-I injection and at 90 minutes (29.8 ± 14.3 ng/ml) after insulin injection. No statistically significant differences between the two GH curves were observed. Serum insulin fell below the limit of sensitivity of the radioimmunoassay (< 8.0 ng/ml) after injection of IGF-I. Glucagon, epinephrine, norepinephrine, cortisol, and lactate levels were similar after both injections. In addition, free fatty acids were suppressed by both hormones, and they reached a nadir 30 minutes after injection. Free fatty acid levels at 60 and 90 minutes, however, were significantly lower ($P < 0.01$) after injection with insulin than with IGF-I.

The authors conclude that IGF-I, when administered in a supraphysiologic dose, is a hypoglycemic agent in human beings. The potency of IGF-I in producing hypoglycemia was 7.5% of that of insulin on a molar basis. The disappearance curve of free IGF-I between 15 and 60 minutes after injection was similar to that of insulin, but the apparent half-life of free IGF-I was twice as long as that of insulin (20 minutes *v* 10 minutes). The authors state that the kinetic features of disappearance of IGF-I are similar to those of insulin in subjects with substantial levels of anti-insulin antibodies. In addition, the effect of free IGF-I on free fatty acids is in keeping with in vitro data obtained in rat adipose tissue, demonstrating that insulin is about 100 times more potent than IGF-I in inhibiting lipolysis. Finally, these data do not support the hypothesis of a negative feedback loop of IGF-I on GH secretion.

Guler H-P, Zapf J, Froesch ER. *N Engl J Med* 1987;317:137-140.

Editor's comment—*This carefully performed study provides much information concerning both the metabolic and the pharmacokinetic effects of recombinant human IGF-I. Further studies will be required to determine the long-term effects of this hormone in individuals with GH deficiency and, possibly, insulin-dependent diabetes.*

WLC

Effect of Growth Hormone Releasing Hormone (GHRH) on Growth Hormone (GH) Secretion in Type II (Non-Insulin-Dependent) Diabetes Mellitus

Pietschmann and Schernthaner studied GH response to GHRH in 21 non-obese and 26 obese patients with Type II diabetes mellitus. Subjects received an intravenous bolus injection of 1 μg/kg GHRH (1-44) following an overnight fast. In addition, nine Type II diabetic patients received hpGHRH during hyperglycemia and after reductions in blood sugar with insulin. The increase in GH levels following GHRH administration was less marked in obese Type II diabetic patients compared to non-obese Type II diabetic patients ($P<0.02$). However, the GH response to GHRH in non-obese Type II diabetic patients was not significantly different from that in control subjects. In addition, reduction in mean fasting plasma glucose values from 247 mg/dl to 131 mg/dl did not influence GH response to GHRH.

Pietschmann P, Schernthaner G. *Diabetologia* 1987;30:13-15.

Editor's comment—*GH response to GHRH in normal subjects has been shown to be influenced by age and obesity. This paper suggests that obesity might be the factor that is predominantly responsible for the GH responses to GHRH in obese Type II diabetics. The authors suggest that GH responses to GHRH may be due to enhanced secretion of hypothalamic somatostatin, since rats with genetic obesity have a greater release of somatostatin from the hypothalamus than do non-obese rats. In addition, the finding that improvement in glucose control does not alter GH response to GHRH is consistent with similar findings in patients with Type I diabetes. Those individuals failed to exhibit glucose-mediated suppression of GHRH-induced GH levels.*

WLC

MEETING CALENDAR

February 16-19, 1988 Joint Meeting of the Western Section of the American Federation of Research and the Western Society for Pediatric Research. Various locations in Carmel, California. Contact: David K. Stevenson, MD, Department of Pediatrics, Room S222, Stanford University School of Medicine, Stanford, CA 94305 (415-723-5711)

February 18-20, 1988 Canadian College of Medical Genetics. Mont Gabriel, Quebec. Contact: Canadian College of Medical Genetics, Alberta Children's Hospital, 1820 Richmond Road SW, Calgary, Alberta T25C7

February 21-25, 1988 15th Annual Seminar in Pediatric Nephrology: Immunosuppression, Growth, and the Neonate. Sheraton-Bal Harbour Hotel, Miami Beach, Florida. Sponsor: Department of Pediatrics, University of Miami. Contact: Pearl Seidler, Division Coordinator, Department of Pediatrics, Division of Pediatric Nephrology, University of Miami School of Medicine, PO Box 016960, Miami, FL 33101 (305-549-6726)

May 2-6, 1988 Annual Meeting of the American Pediatric Society/ Society for Pediatric Research. Sheraton Hotel, Washington, DC. Contact: Debbie Wogenrich, Executive Director, Society for Pediatric Research, 2350 Alamo SE, Suite 106, Albuquerque, NM 87106 (505-764-9099)

May 6, 1988 Annual Scientific Session, Lawson Wilkins Pediatric Endocrine Society. Sheraton Hotel, Washington, DC. Contact: Debbie Wogenrich, Executive Director, Society for Pediatric Research, 2350 Alamo SE, Suite 106, Albuquerque, NM 87106 (505-764-9099)

May 9-13, 1988 Clinical Disorders of Bone and Mineral Metabolism. Detroit, Michigan. Sponsor: Henry Ford Bone and Joint Specialty Center. Contact: Henry Ford Hospital, Continuing Medical Education, 2799 West Grand Boulevard, Detroit, MI 48202 (800-662-8242, within Michigan; 800-521-7946, other states and international)

June 8-10, 1988 70th Annual Meeting of The Endocrine Society. New Orleans, Louisiana. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

July 10-13, 1988 20th Anniversary of the Clinical Genetics Conference. Baltimore, Maryland.

July 17-23, 1988 8th International Congress of Endocrinology. Kyoto, Japan. Contact: Travel Planners—Kyoto Congress, Suite 150, GPM Building, San Antonio, TX 78216-5674 (512-341-8131)

July 20-23, 1988 15th International Auxology Congress. Exeter University, Exeter, England. Contact: Prof. J.M. Tanner, Room 115, Institute of Child Health, 30 Guilford Street, London, England WC1N 1EH

Growth, Genetics, and Hormones is published under an educational grant from Genentech, Inc.

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